

A - Background for Peer Reviewers

Dear Peer Reviewer,

Thank you for agreeing to review this 2012 Final (Post Public Comment) version of the phosphate ester flame retardant (PEFR) toxicological profile. We also thank you for reviewing the previous 2009 Draft for Public Comment version. Because you have reviewed the previous (2009) version of this profile and because a only few changes were made to that 2009 version following the public comments, we are providing a detailed 'Charge' which focuses your review on just those 'new' aspects in the 2012 version, predominately the new substance, TCP.

Historical Info

Reducing the risk from fires has been achieved by using a wide variety of 'flame retardant' (FR) substances over several decades. However, each group of those substances has not been without their own potential health risks. The National Academy Press recently published an evaluation of the risks associated with the wide breadth of those substances (NAP 2000). As a larger group of FRs, the PBDEs have lost favor (ATSDR 2004) and newer replacements have been sought. A group receiving increasing interest is the phosphate ester flame retardants (PEFRs).

Collectively, some phosphate esters (PE) have been used for over 50 years as plasticizers (in nitrocellulose, acrylate lacquers, and varnishes), as waterproofing agents, and as lubricants and hydraulic fluids. In fact, a number of these PE substances have already been reviewed in the ATSDR tox profile on hydraulic fluids (ATSDR 1997). Thus, although some PEs do not have flame retardant properties, select ones do and these PEs are being reevaluated for use as FRs. Simultaneously, newer PEs continue to be developed and tested as FRs.

Finally, it is very important to note that because of their chemical structure the PEs can also be called organophosphate esters (OPs). However, one must be careful to not confuse these PEFR substances with the larger, more well-known group of OPs, namely the OP pesticides and nerve agents. The organic component (PE moiety) of the PEs used as FRs makes them very different from the OP pesticides, chemically and biologically.

Toxicological Profiles (TPs)

As noted above, the ATSDR TP on hydraulic fluids has previously reviewed several of the PEs. In contrast, this PEFR TP focuses on just those PEs used as flame retardants.

The previous PEFR TP version (Draft for Public Comment, ATSDR 2009) focused on seven PEFRs that had the most interest for commercial use in various consumer products. In that TP, there were nine different MRLs derived for those seven PEFRs (see Table 1, further below).

However, this 2012 version (Final) of the PEFR TP has added an eighth substance, tricresylphosphate (TCP), because of the historical interest in it as a well-known toxicant. For TCP we were able to derive two additional (new) MRL values. All the MRL values are shown in Table 1 (for your easy reference).

General References

ATSDR 1997	http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=757&tid=141
ATSDR 2004	http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=529&tid=94
ATSDR 2009	http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1119&tid=239
NAP 2000	http://www.nap.edu/openbook.php?record_id=9841

B - Charge to Peer Reviewers

ATSDR Toxicological Profile for Phosphate Ester Flame Retardants Profile and Minimal Risk Level Review

As noted above, we are asking you to review only specific parts of this 2012 version of the profile (as explained below), because you had reviewed the 2009 version and because only focused changes have been made to the 2009 version. In particular, we have added one new substance (with two new MRLs) and revised four of the previous nine MRLs.

1 – New TCP Substance

Please review the only text of the profile which discusses the various health effects of the one newly-added substance, tricresyl phosphate, TCP. A table (Table 2) is provided in Part C (below), which lists all those Sections and page numbers. You may choose to scan, search or read the whole profile, or you may use the table of specific page numbers, but in either case we ask for you focus your comments only on that text pertaining to TCP.

2 – New TCP MRLs

Please review closely the two new Minimal Risk Levels (MRLs) that were derived for the new substance, TCP. This is the only new substance that was added to the 2009 profile and only two new MRLs have been derived for TCP (see below). No other new MRLs were derived since 2009.

Please review the MRL discussions and derivations for TCP, specifically, the MRL Worksheets (Appendix A), the MRL Rationale Statements, and the MRL presentation in Chapter 2.3 of the profile text. Please provide specific comments on those two new TCP MRLs as to the following five questions:

- 1 – Are the discussions of the new MRLs logical and clear?
- 2 – Are the study and endpoint selection appropriate?
- 3 – Is the application of the PBPK model appropriate?
- 4 – Are you aware of other studies that would impact the MRLs?
- 5 – Do you concur with the MRLs as derived?

Summary of Two New MRLs for TCP

Intermediate-Duration Exposure

ATSDR has derived an MRL of **0.04 mg/kg/day** for intermediate-duration exposure (15 to 364 days) to TCP. This MRL is based on a study by NTP 1994 that exposed Fisher 344 rats to TCP for 104 weeks. A PBPK model was used to predict the point of departure for several endpoints. The most sensitive endpoint selected was for ovarian lesions in female rats at a 3 month time point. The model resulted in a BMDL10 of 3.72 mg/kg/day, which when divided by the uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), gives an MRL of 0.04 mg/kg/day.

Chronic-Duration Exposure

ATSDR has derived an MRL of **0.02 mg/kg/day** for chronic-duration exposure (equal to or more than 365 days) to TCP. This MRL is based on a study by NTP 1994 that exposed Fisher 344 rats to TCP for 104 weeks. A PBPK model was used to predict the point of departure for several endpoints. The most sensitive endpoint selected was for ovarian lesions in female rats at a 15 month time point. The model resulted in a

BMDL10 of 2.12 mg/kg/day, which when divided by the uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), gives an MRL of 0.02 mg/kg/day.

3 – Revised MRLs

Just like we are not asking you to review the whole profile again (see above), we are also not asking you to review all nine previous MRLs in the 2009 version. Instead, please review only those four ‘revised’ MRLs that are discussed next.

In the previous 2009 profile, as noted, a total of nine MRLs were derived for the seven substances included in that profile. Between 2009 and the finalizing of this 2012 version, a newer version of PBPK modeling software became available and all nine of those previous MRLs were reexamined. This resulted in the slight revision of four of those nine MRL values. Note – in all nine previous MRLs, including the four that have changed (ever so slightly), the same scientific study and the same endpoints that had been selected in the 2009 profile were still used in the 2012 version. However, in the case of four of the MRLs the ‘best fitting model’ changed and this resulted in a slightly revised MRL value. The four ‘revised’ MRLs are summarized below and in Table 1.

Again, we are not asking you to review all nine previous MRLs. Instead, please focus on only those four ‘revised’ MRLs noted below (their MRL Worksheet page number is noted below and in Table 1). Furthermore, because you have previously reviewed the 2009 version of the MRL Worksheets, we remind you that no changes have been made to the study used, the endpoint selected or the use of PBPK modeling, itself, for any of the nine MRLs. All the studies, endpoints and use of PBPK modeling that were deemed appropriate in the 2009 version remain the same. Only the final model that was selected has changed in the four ‘revised’ cases. Thus, we ask you to address only these two questions concerning those four ‘revised’ MRLs:

- 1 – Are the discussions of the four ‘revised’ MRLs still logical and clear?
- 2 – Do you concur with the four revised MRLs as derived?

Again, please address the above two question for only these four revised MRLs:

TCEP	chronic-duration	Worksheet page A-8
TnBP	intermediate-duration	Worksheet page A-18
TnBP	chronic-duration	Worksheet page A-23
TBEP	intermediate-duration	Worksheet page A-31

4 – Information Provided

There are three tables of ‘detailed’ information provided in Part C, below, to facilitate your review.

Included in your packet is a copy of the 2012 ASTDR profile (in PDF format) for review. That PDF file contains the full text, all the Tables and Figures, as well as all the MRL Worksheets (in Appendix A). The ‘MRL Rationale Statements’ for the six selected MRLs (two new, four revised) that we also solicit specific comments on are provided in a separate MS Word file. Finally, we have also included a copy (in PDF format) of the study (NTP 1994) that was used to derive the two new TCP MRLs.

Please submit your comments electronically in MS Word to ATSDR.

Please contact ATSDR if you have any questions.

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C – Detailed Information for Peer Reviewers

Below are three tables that are provided to facilitate your review.

Table 1 presents a summary, on one viewable page, of all the MRLs associated with this 2012 profile. The top part of Table 1 (Part 1) presents the actual MRL values (for a total of eleven MRLs) for all eight different substances that are presented in the 2012 profile. As was discussed above (in the charge), please focus on the two new TCP MRLs and the four 'revised' MRLs. The bottom part of Table 1 (Part 2) presents a quick summary of the endpoints, the BMDL10 values, and the 2009 values for the four 'revised' MRLs, as well as for the two new TCP MRLs.

Table 2 presents a listing of all the places (page numbers) in the 2012 profile (provided as a PDF file) where the new substance, TCP is discussed. The top of Table 2 contains additional information explaining that Table.

Table 3 presents a listing of the page numbers in the MRL Rationale Statement document (provided as an MS Word file) for only the six MRLs (four revised, two new) that are to be reviewed in that document

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Table 1 Phosphate Ester Flame Retardants (PEFRs) – MRL Values – 2012

Part 1 List of All PEFR Profile Substances and MRLs All MRL values are oral in mg/kg/day (m/k/d)

Year	Abbreviation	R = [where (R-O) ₃ -P=O]	Acute	Intermediate (I)	Chronic (C)
-----	-----	-----	-----	-----	-----
2009 =>					
	TCEP	tris (2-chloroethyl)		0.6	0.2 * (A-8)
	TnBP	tri butyl	1.1	0.08 * (A-18)	0.08 * (A-23)
	TBEP	tris (2-butoxyethyl)	4.8	0.09 * (A-31)	
	TDCP	tris (1,3-dichloro, 2-propyl)		0.05	0.02
	TPP	tri phenyl			
	TiBP	tri isobutyl			
	TCP	tris (2-chloroisopropyl)			
2012 (new) =>					
	TCP **	tri cresyl		0.04 ** (A-48)	0.02 ** (A-53)

* Four of the MRL values from the 2009 Profile were revised after using additional PBPK models.

** Two new TCP MRLs were derived and are being added to the 2012 Profile.

() The number parenthesis is the page number for the MRL Worksheet in Appendix A.

Part 2 MRL Endpoints and Values (m/k/d) for the * Revised (from 2009) and the ** New (2012 TCP) MRLs

* TCEP – C – 0.2	BMDL10 of 32.82 m/k/d for renal tubule epithelial hyperplasia in female rats – NTP 1991a [2009 had been an MRL of 0.3 using BMDL10 of 36.09 m/k/d]
* TnBP – I – 0.08	BMDL10 of 8.03 m/k/d for urinary bladder hyperplasia in male rats in 10-week dietary study [2009 had been an MRL of 0.02 using BMDL10 of 1.96 m/k/d] Arnold et al 1997
* TnBP – C – 0.08	Intermediate used by default when compared to BMDL10 chronic value (Auletta 1998a, b) [2009 had been an MRL of 0.02 via using intermediate value protective]
* TBEP – I – 0.09	BMDL10 of 8.88 m/k/d for hepatocyte vacuolization in male rats 18 wk diet – Reyna 1987a [2009 had been an MRL of 0.2 using BMDL10 of 21.92 m/k/d]
** TCP – I – 0.04	BMDL10 of 3.72 m/k/d for ovarian lesions in female rats – NTP 1994 [2012 new substance and new MRL]
** TCP – C – 0.02	BMDL10 of 2.12 m/k/d for ovarian lesions in female rats – NTP 1994 [2012 new substance and new MRL]

Table 2 TCP ‘Discussions’ in 2012 Profile

This table presents a listing of all the places in the 2012 profile (see PDF provided) where the new substance, TCP, is mentioned or discussed, including the various Tables and the MRL Worksheets. Obviously, you can use a global ‘find’ for TCP to give a similar result. However, this Table is designed to make it easier for you to find certain aspects more quickly and use as a check list, if desired. In a few cases a couple of additional pages are included that give a bigger picture on the topic.

As noted in the ‘charge,’ we ask that you focus only on the new substance, TCP, particularly its two new MRLs, along with some attention to the four revised MRLs.

Profile Section	Profile Page, Lines – Comments				
1.1 PHS	pp1 to 8, all – overview of profile – the Public Health Statement (PHS)				
2.1 Background	p9, all				
2.2 Summary	p10, lines 25 – 29				
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
	p24	TnBP	intermediate	revised *	0.02 => 0.08
	p26	TnBP	chronic	revised *	0.02 => 0.08
	p29	TBEP	intermediate	revised *	0.2 => 0.09
				(2012) mg/kg/day	
	p34	TCP	intermediate	new * *	0.04
	p35	TCP	chronic	new * *	0.02
	p 34, line 1 to p37, line 25 – specific discussion of TCP MRLs				
3.0 Health Effects					
3.2.1.1	p43, lines 15-26				
3.2.2.1	p52, lines 20-53				
	pp106-131	LSEs for TCP – Table 3-6, Figure 3-6			
	p139, lines 10-21				
	p139, lines 13-28				
	p140, lines 20-27				
	p141, lines 19-28				
	p144, line 25 to p145, line 8				
	p147, line 28 to p148, line 4				
	p148, line 12 to p149, line 21				
	p151, lines 25-34				

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

	<p>p155, lines 1-19</p> <p>p157, line 23 to p158, line 34</p> <p>p161, line 1 to p162, line 32</p> <p>p165, lines 17-30</p> <p>p168, lines 24-29</p> <p>p169, lines 20-29</p> <p>p179, lines 26-28</p> <p>p180, lines 19-20</p> <p>p180, line 33 to p181, line 3</p>	
3.3	<p>p182, line 32</p> <p>p183</p> <p>p185</p> <p>p188, line 15</p>	<p>Genotoxicity, mention being in Table 3-9</p> <p>Table 3-9 – Genotoxicity</p> <p>Table 3-9 – Genotoxicity</p>
3.4	<p>p189, lines 32-33</p> <p>p190, lines 7-12</p> <p>p191, lines 18-22</p> <p>p194, line 23 to p195, line 2</p> <p>p196, lines 28-32</p> <p>p205, lines 1-13</p>	<p>Toxicokinetics</p>
	<p>p206</p> <p>p208, lines 9-25</p> <p>p210, lines 16-21</p>	<p>Figure 3-12 – Proposed Metabolic Pathways</p>
3.5	<p>p215, lines 1-10</p> <p>p215, lines 21-25</p> <p>p217, line 18 to p218, line 31</p> <p>p219, lines 9-10</p> <p>p223, lines 21-26</p> <p>p227, lines 19-22</p> <p>p231, line 33 to p232, line 3</p> <p>p233, lines 4-5</p> <p>p234, lines 7-9</p> <p>p236, lines 11-13</p> <p>p236, lines 32-34</p> <p>p237, lines 9-15</p> <p>p237, line 17</p> <p>p237, line 34 to p238, line 6</p>	<p>Mechanism of Action</p>
4.0 Chemical and Physical Info		
4.1	Identity	Overview, interesting background info
4.2	<p>p245, in Table 4-1</p> <p>p248, in Table 4-2</p>	
5.0 Production, Import. Use		
5.1	<p>p250, lines 11-13</p> <p>p251, line 4</p> <p>p252, in Table 5-1</p> <p>p253, line 33</p>	

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

6.0 Potential for Human Exposure

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

7.0 Analytical Methods

7.2 p285, in Table 7-2

8.0 Regulations

p290 and pp295-6 Summary of all MRLs

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
Revised	TnBP	intermediate	0.02 (2009) => 0.08 (2012)	A-18
Revised	TnBP	chronic	0.02 (2009) => 0.08 (2012)	A-23
Revised	TBEP	intermediate	0.2 (2009) => 0.09 (2012)	A-31
New	TCP	intermediate	0.04 (2012)	A-48
New	TCP	chronic	0.02 (2012)	A-53

* 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.

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	Revised
8	TnBP intermediate-duration	Revised
15	TnBP chronic-duration	Revised
18	TBEP intermediate-duration	Revised
24	TCP intermediate-duration	New
31	TCP chronic-duration	New

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