MEMORANDUM:

DATE: May 7, 1996

TO: The File

FROM: Monica A. Barron, Ph.D.
Toxicologist

SUBJ: Peer Reviewer Comments

EPA acknowledges the numerous detailed comments provided by the reviewers, and has addressed substantive issues in the Public Comment Summary and Response Document in lieu of revising the background document, due to resource constraints. This memorandum addresses the peer reviewers' substantive comments on the Organobromines Final Rule background materials. Since the background document is not being revised, editorial comments are not addressed. Each reviewer's comments are addressed individually, followed by an EPA response on how the comments were resolved for the Final Rule.

1) Summary of Comments Received from Richard J. Bull, Ph.D., Battelle Pacific Northwest Laboratories, Richland, Washington

Dr. Bull addressed the EPA issue question "Is the SAR analysis for 2,4,6-TCP sufficiently rigorous to be considered scientifically defensible?" Dr. Bull focused on the Risk Assessment Background Document which provided a justification for the use of a QSAR rather than reviewing the Public Comment Summary and Response Document which provided a rationale for the use of a qualitative SAR. Nevertheless, he felt that a qualitative rather than a quantitative SAR was appropriate and sufficent for the Agency's decision to list wastes containing TBP. Much of Dr. Bull's response centers on a review of available mutagenicity data on TCP and its application to TBP; he recommended that EPA review a 1977 article by Rasanen *et al* for additional information on the mutagenicity of TCP with and without activation.

EPA agrees with the commenter that the use of a qualitative rather than a qantitative SAR is most appropriate for this Final Rule. Several of the issues Dr. Bull raised about the mutagenicity of TCP were adressed in the Public Comment Summary and Response Document. However, EPA appreciates his comments on the potential mechanism of action of the carcinogen TCP and its relationship to TBP. Dr. Bull did not have any additional toxicological data to add to the document. The Rasanen article has been retrieved and reviewed,and data from the article on the mutagenicity of 2,4,6-TBP have been incorporated into the Public

Comment Summary and Response Document The Rasanen data showed that 2,4,6-TCP was also negative in another *Salmonella* assay conducted in the presence and absence of rat S9.

2) Summary of Comments Received from James R. Olson, Ph.D., Department of Pharmacology and Toxicology, SUNY at Buffalo, NY

Dr. Olson provided comments on the Risk Assessment Background Document as well as the Public Comment Summary and Response Document. On the latter, he indicated that he favors the use of a qualitative SAR rather than a QSAR as a scientificallly defensible method for developing a human health reference value for TBP. He also believes that TCP is the most appropriate surrogate for TBP based on structural similarities. He further states that the references to other chlorine/bromine analogs support the use of TCP as a surrogate for TBP. He said that the cancer potency factor for TCP was an appropriate value to use for TBP, given that TBP data that would allow for the development of an independent number of adjustments to the TCP value are not available. Dr. Olson recommended that genotoxicity and mutagenicity information, including mechanistic data, would greatly the document, but he was unable to provide this data for either TCP or TBP.

EPA has no response to Dr. Olson's comments and is appreciative of his review of the materials and his agreement with the use of a qualitative SAR using TCP as a surrogate for TBP.

3) Summary of Comments Received from Dale Hattis, Ph.D., CENTED, Clark University, Worster, MA

Dr. Hattis provided substantial comments on the Public Comment Summary and Response Document. He favored the use of a qualitative rather than a quantitative SAR. He felt it was appropriate to use the TCP cancer potency factor as a default value for TBP; however, he indicated that he agreed with public commenter #7 that the cancer potency factor for TCP should be adjusted to account for the molecular weight of the compounds (assuming a 1:1 relationship on a molar basis, rather than on a weight basis). Dr. Hattis stressed that the analysis in the document should address how brominated and chlorinated compounds differ in their toxic effects and how the potency of TBP should be estimated based on TCP. Based on reproductive and developmental studies, he stated that it appears that TBP is likely to be equal to or less toxic than TCP, and he supplied several papers that supported this conclusion.

EPA appreciates the effort Dr. Hattis made in providing additional information that supports EPA's use of TCP as a surrogate for TBP. EPA agrees with Dr. Hattis' recommendation to revise the cancer potency factor for TBP to reflect the different molecular weight of the compound compared with TCP. Therefore, based on a molecular weight of 331 for TBP, the cancer potency factor of 1.1×10^{-2} mg/kg/day for TCP (molecular weight 197) will be adjusted to 6.5×10^{-3} mg/kg/day. Based on this adjustment, the estimated individual risk from TBP in the off-specification

product would be reduced from $7x10^{-4}$ to $4x10^{-4}$, still above levels of concern. EPA has reviewed the studies suggested by Dr. Hattis on the reproductive/developmental effects and comparative potency of bromo- and chlorophenols. These studies suggest that brominated phenols are likely to be slightly less toxic than chlorophenols in producing developmental effects, when doses are expressed on a molar basis. Calculations by the peer reviewer did not reveal a statistically significant difference between potency of the chlorophenol and bromophenol. Although the endpoint evaluated by these papers (reproductive/developmental toxicity) is different than the endpoint of concern for this Rulemaking (carcinogenicity), the results on relative potency are likely to be applicable to both endpoints, since toxicity in both cases is likely to be attributable to a toxic metabolite. In addition, Dr. Hattis noted that toxic potency is roughly correlated with cancer potency. Thus, the data on developmental toxicity of halogenated phenols support the adjustment of the TCP CSF to account for the differences in molecular weight between TCP and TBP.

Dr. Hattis also discussed a paper by Juhl *et al* (1991) which describes a mechanism of action for the DNA damage caused by TCP. This paper is a sequel to a previous paper by Juhl *et al* (1989) which proposed an alternative mechanism of action for TCP and which was cited in the background document Development of Provisional Human Health Reference Value for 2,4,6-Tribromophenol. He also provided references to several other papers that contain additional information on the toxicity of other halogenated phenols and related compounds.

The in-depth review provided by Dr. Hattis is appreciated by EPA. Although EPA had included the earlier paper by Juhl in the Development of Provisional Human Health Reference Value for 2,4,5-Tribromophenol, the 1991 Juhl paper had not been included. EPA has reviewed the 1991 Juhl paper, which analyzed metabolites and DNA reactivity of 2,4,5-TCP. Both this paper and the 1989 Juhl *et al* paper provide data supporting the genotoxicity of trichlorophenols. Differences in the mechanism proposed by the two papers may be related to the fact that the initial paper addressed 2,4,6-TCP while the latter paper addressed the related compound 2,4,5-TCP. Either way, the data provided in these papers are insufficient to further refine the 2,4,6-TCP assessment. While the other papers listed by Dr. Hattis are interesting, they do not provide additional information on adjusting the TCP cancer potency for TBP, nor do they provide other toxicological information that may be directly applicable to TBP. The additional papers are not included in the revised Public Comment Summary and Response Document.

Peer Reviewer Summary

EPA is pleased that all three peer reviewers agreed that a qualitative structure-activity

relationship was more appropriate for this Final Rule than a quantitative SAR. In addition, two of the three reviewers recommended the use of TCP as the most appropriate surrogate for TBP and that the cancer potency factor for TCP was appropriate as a default value for TBP. The third reviewer suggested that the TBP potency factor be adjusted to reflect the different molecular weights of the two compounds. The following modifications were made to the Public Comment Summary and Response Document: (1) a relatively minor change (based on molecular weight differences) to the cancer potency factor for TBP, and (2) a discussion of the relative reproductive/developmental effects of chlorinated versus brominated compounds, was added. The latter topic is helpful in supporting EPA's position on the use of TCP as a surrogate for TBP and the possible potency of the two compounds, but it is not critical to the substance of the document.