FINAL PEER REVIEW SUMMARY REPORT

External Peer Review of the EPA/IRIS Draft Report *Toxicological Review of Pentachlorophenol (CASRN 87-86-5)*

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I. INTRODUCTION

The Integrated Risk Information System (IRIS) is an EPA database of potential adverse human health effects that may result from chronic (or lifetime) exposure, or in select cases less-than-lifetime exposures, to chemicals in the environment. IRIS currently provides health effects information on over 500 chemical substances.

IRIS contains chemical-specific summaries of qualitative and quantitative health information in support of two steps of the risk assessment process, i.e., hazard identification and dose-response evaluation. IRIS information includes a reference dose (RfD) for noncancer health effects resulting from oral exposure, a reference concentration (RfC) for noncancer health effects resulting from inhalation exposure, and an assessment of carcinogenicity for both oral and inhalation exposures. Combined with specific situational exposure assessment information, the health hazard information in IRIS may be used as a source in evaluating potential public health risks from environmental contaminants.

The IRIS program within EPA's National Center for Environmental Assessment (NCEA) developed a Toxicological Review of pentachlorophenol, which updates an assessment that was posted to the IRIS database in 1991. Pentachlorophenol was nominated for reassessment by EPA's Office of Pesticides Program (OPP) to support the development of the Registration Eligibility Decision (RED) document for reassessment of pesticides registered prior to 1984 under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The draft document slated for the external peer review contains a chronic oral RfD and a quantitative cancer assessment.

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II. CHARGE TO THE REVIEWERS

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of pentachlorophenol (PCP) that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). An existing IRIS assessment of PCP was posted to the database in 1987 and a cancer assessment was added in 1991.

The current draft health assessment includes a chronic reference dose (RfD) and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of PCP. Please provide detailed explanations for responses to the charge questions.

(A) General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazard?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of PCP.

3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of PCP.

4. Please comment on the identification and characterization of source of uncertainty in Sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Chemical-Specific Charge Questions:

(B) Oral reference dose (RfD) for Pentachlorophenol

1. A 1-year oral study in dogs by Mecler (1996) was selected as the basis for the RfD. Please comment on whether the selection of this study as the principal study is scientifically justified. Has this study been transparently and objectively described in the document? Are the criteria and rationale for this selection transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. An increase in hepatic effects (characterized by a dose-related increase in the incidence of hepatocellular pigmentation, cytoplasmic vacuolation, chronic inflammation, and severely discolored livers; statistically significant increases in absolute (females only) and relative liver weights, and serum enzyme activity) as reported by Mecler (1996) was selected as the critical effect for the RfD because these effects are considered by EPA to be indicative of hepatocellular injury. Please comment on whether the rationale for the selection of this critical effect is scientifically justified. Are the criteria and rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. The hepatotoxic data and a NOAEL/LOAEL approach were used to derive the point of departure (POD) for the RfD. Please provide comments with regard to whether this is the best approach for determining the POD. Has it been transparently and objectively described? Please identify and provide rationales for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. The RfD is based on toxic effects observed in dogs (Mecler, 1996) administered a technical grade formulation of PCP (90.9% purity). Considering the toxicological database for PCP is largely comprised of studies that utilized similar formulations, as well as commercial and analytical (pure) formulations, please provide comments with regard to whether the use of data based on animal exposure to a technical grade PCP formulation of this purity is the best approach and can be considered representative of pure PCP. If not, please identify and provide the rationale for any alternative data sets, and the sufficiency of such data sets, to support derivation of the RfD.

5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the document? If changes to the uncertainty factors are proposed, please identify and provide a rationale(s). Please comment specifically on the following uncertainty factor:

- An uncertainty factor of 3 was applied in deriving the RfD to account for the use of a LOAEL rather than a NOAEL as the POD.

(C) Inhalation reference concentration (RfC) for Pentachlorophenol

1. An RfC was not derived due to the lack of available studies to characterize the health effects associated with pentachlorophenol administered via the inhalation route. Are there available data that might support development of an RfC for pentachlorophenol?

(D) Carcinogenicity of Pentachlorophenol

1. Under EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that pentachlorophenol is *likely*

to be carcinogenic to humans. Please comment on the cancer weight of evidence characterization. Has the scientific justification for the weight of evidence descriptor been sufficiently, transparently and objectively described? Do the available data for liver, adrenal gland, and circulatory system tumors in mice and nasal tumors and mesotheliomas in rats support the conclusion that PCP is a likely human carcinogen?

2. A quantitative oral cancer assessment has been derived for PCP. Do the data support an estimation of a cancer slope factor for PCP? Please comment on the scientific justification for deriving a quantitative cancer assessment. Has the rationale and scientific justification for quantitation been transparently and objectively described?

3. A two-year oral cancer bioassay (NTP, 1989) in mice was selected as the principal study for the development of an oral slope factor. Please comment on the appropriateness of the selection of the principal study. Has the rationale for this choice been transparently and objectively described?

4. Data on the mode of action (MOA) of carcinogenicity of PCP was considered. Several hypothesized MOAs were evaluated within the Toxicological Review and EPA reached the conclusion that a MOA(s) could not be supported for any tumor types observed in animal models. Please comment on whether the weight of the scientific evidence supports this conclusion. Please comment on whether the rationale for this conclusion has been transparently and objectively described. Please comment on data available for PCP that may provide significant biological support for a MOA beyond what has been described in the Toxicological Review.

5. Increased incidence of tumors in male and female B6C3F_1 mice was observed following administration of two formulations of PCP (technical grade PCP and EC-7 [a commercial grade of PCP]) that contain various chlorophenol and chlorinated dibenzodioxin and dibenzofuran contaminants. The carcinogenic contributions of PCP versus those of contaminants have been described qualitatively and to a limited extent quantitatively within the document. The cancer assessment is based on the data sets resulting from exposure to two different formulations that are approximately 90% PCP, with the assumption that carcinogenic contributions from the contaminants are minimal. Please comment on the scientific justification and transparency of this analysis. Please comment on whether these are the appropriate data sets on which to base the cancer risk estimate and, if not, please identify and provide the rationale for any alternative data sets, and the sufficiency of such data sets, to support estimation of cancer risk.

6. Data on tumors in the liver and adrenal gland in B6C3F_1 male mice administered technical PCP were used to estimate the oral cancer slope factor. Please comment on the estimation of a statistically appropriate upper bound on total risk (combined slope factor), which describes the risk of developing any combination of tumor types considered. Please comment on the scientific justification and transparency of the analysis for combining these data to derive the oral cancer slope factor. Please comment on the use of data in male mice exposed to technical PCP for a cancer risk estimate for both technical and analytical PCP.

III. GENERAL IMPRESSIONS

Scott M. Bartell

I have questions regarding some specific points and decisions made for dose-response modeling, but in general the report is clear, and very detailed. In general the draft appears to draw sound conclusions, but there are some debatable approaches used in the derivation of the RfD and for the slope factor for combined tumor sites. Some of the information is needlessly repeated in different sections of the report (e.g., tables appearing in both the main report and the appendices).

I am not a toxicologist or subject expert in pentachlorophenol, so I cannot evaluate the accuracy of the literature review on these topics. The following comments are focused on PCP dose-response modeling and uncertainty analysis.

Nasrin Begum

The report of the Draft Document "Toxicological Review of Pentachlorophenol" contains many study reports. Most are essentially synopses of the studies that were completed. Most of them appear to contain the essentials of the study originally completed and reported to the Agency. However, there are a few things in these synopses that make them a little difficult to read at first glance, such as leaving out the adjectives and pronouns which tend to smooth out the speech of the narrative. There have occasionally been words left out that, when added, may improve the understanding of the sentences in which it was done.

Leslie T. Stayner

The EPA is to be commended for producing an extremely well written document, and a thorough review of the epidemiologic and toxicological literature concerning the potential health hazards associated with PCP. The document also presents a clear basis for its determination of hazard identification and dose-response analysis. I do have a few criticisms of the report but they are, for the most part major, and are described in the following sections.

Paul B. Tchounwou

The document represents a comprehensive review of the toxicology of pentachlorophenol. It has been produced by the U.S. Environmental Protection Agency to provide a scientific basis and justification for updating the Integrated Risk Information System (IRIS) regarding the systemic and carcinogenic effects of pentachlorophenol. It is an authoritative document that provides a thorough overview of the toxicology of pentachlorophenol. It reviews relevant and critical studies that have been performed on pentachlorophenol with regard to its chemical formulations and physico-chemical

properties; toxico-kinetics in terms of absorption, distribution, metabolism, and excretion; and toxic effects on humans and experimental animals.

A special emphasis is placed on the health risk assessment of pentachlorophenol, with in-depth evaluations and discussions of available scientific data related to hazard identification, dose-response assessment, exposure assessment and risk characterization. The document also provides major conclusions in the characterization of hazard associated with pentachlorophenol exposure, based on a critical review and a thorough evaluation of epidemiological studies in occupationally exposed populations, and toxicological investigations with experimental animals.

The information provided is very accurate. It is also well written and clearly presented. The conclusions are supported by the published scientific literature, and in accordance with national and international risk assessment guidelines.

Gary M. Williams

The Toxicological Review is comprehensive, but some of the scientific evidence is not objectively represented.

IV. RESPONSE TO CHARGE QUESTIONS

(A) General Charge Questions

1. Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazard?

Scott M. Bartell

The toxicological review is quite logical and clear. It could be more concise, as some information appears to be repeated in different sections of the document.

Nasrin Begum

This reviewer believes that the studies have, for the most part, been accurately, clearly and objectively represented. The great amount of data and varied aspects of the toxicity of PCP, while presented as synopses with the final results, have fairly well synthesized the cancer and non-cancer hazard. The synopses, however, do have some limitations which include: grammar use, misplaced decimals and a few extremely lengthy sentences. Only one or two instances of incomplete thoughts were noted in the study write-ups.

Leslie T. Stayner

The toxicological and epidemiologic review is very logical, clear and concise. I am not familiar with the toxicological literature so I can't comment on whether the review objectively summarized the evidence. The epidemiologic review is to my knowledge is complete and well represented by the review except for some new studies that are described below.

Paul B. Tchounwou

The Toxicological Review of Pentachlorophenol is presented in a logical fashion. It starts with a Table of Contents that lists the major sections including introduction; chemical and physical properties relevant to assessments; toxicokinetics (absorption, metabolisms, distribution and excretion); hazard identification (human studies, experimental studies, reproductive and developmental studies, other endpoints, mechanistic studies, non cancer effects, cancer effects, susceptibility); dose-response assessment (oral reference dose, inhalation reference concentration, cancer assessment); and major conclusions in hazard characterization (human hazard and dose-response), references, and appendices. The lists of tables, figures, and abbreviations are also provided. EPA has done an excellent job with this review which in my opinion is very comprehensive. The scientific evidence from the published literature is thoroughly reviewed. The weight of evidence of pentachlorophenol toxicity is objectively analyzed with regard to its carcinogenic (systemic) and carcinogenic end-points. The derivation of PODs, RfDs, RfCs, and cancer

slope factors were based on the available scientific data. Also, reasonable assumptions were made in the derivations of these parameters.

Gary M. Williams

The organization of Toxicological Review is cumbersome. The scientific evidence is not adequately evaluated, regarding the evaluation of Mode of Action (MOA). Specifically the initiation/promotion study of Umemura et al (1979) should be incorporated into assessment of the MOA for liver tumors.

(A) General Charge Questions

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of PCP.

Scott M. Bartell

I am not aware of any such studies.

Nasrin Begum

This reviewer is not aware of any additional studies which should be considered in the assessments since no request for additional literature searches were made.

Leslie T. Stayner

There is a new NIOSH study that provides additional evidence for an association between PCP exposure and the risk of NHL (Ruder and Sweeney, 2009). Unfortunately, at this time, a conference abstract is all that is available for the study, but my understanding from communicating with the author is that a full manuscript may be available later this summer.

Another recently published paper that I found to be missing from the review is a study by McLean et al. (2009) on morbidity among former New Zealand sawmill workers exposed to PCP. This study provides evidence of a significant association with PCP and several physical neuropsychological effects.

I have also found a paper that was published earlier and should have been included in the review. It was a case-control study of nasal and nasopharyngeal cancer that found an association with exposure to chlorophenols (Mirabelli et al., 2000).

Paul B. Tchounwou

All relevant studies, updated to December 2008, have been considered. The only additional studies may involve those published in 2009, and may include the following new publications:

Folch J, Yeste-Velasco M, Alvira D, de la Torre AV, Bordas M, López M, Sureda FX, Rimbau V, Camins A, Pallàs M. Evaluation of pathways involved in pentachlorophenol-induced apoptosis in rat neurons. Neurotoxicology. 2009 May;30(3):451-458.

Orton F, Lutz I, Kloas W, Routledge EJ. Endocrine disrupting effects of herbicides and pentachlorophenol: in vitro and in vivo evidence. Environ Sci Technol. 2009 Mar 15;43(6):2144-2150.

Zhu BZ, Shan GQ. Potential mechanism for pentachlorophenol-induced carcinogenicity: a novel mechanism for metal-independent production of hydroxyl radicals. Chem Res Toxicol. 2009 Jun;22(6):969-977.

McLean D, Eng A, Walls C, Dryson E, Harawira J, Cheng S, Wong KC, 't Mannetje A, Gray M, Shoemack P, Smith A, Pearce N. Serum dioxin levels in former New Zealand sawmill workers twenty years after exposure to pentachlorophenol (PCP) ceased. Chemosphere. 2009 Feb;74(7):962-967.

Gary M. Williams

Comparison of mouse and rat liver effects. The mouse liver tumor promotion and lack of initiation findings of Umemura *et al.* (1999) (Section 4.2.4.1.1) need to be incorporated in the MOA section (4.5) and addressed in 4.7.3.

(A) General Charge Questions

3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of PCP.

Scott M. Bartell

More information on PCP metabolism and the mode(s) of action for PCP carcinogenicity, particularly pertaining to humans, would likely be informative in future assessments. Future epidemiologic studies should focus on fully quantitative exposure assessment, adjustment for non-PCP occupational exposures, and identification/measurement of precursor events in PCP induced carcinogenesis.

Nasrin Begum

This reviewer would consider some additional metabolism studies comparing the pathways of humans with the several animal species which produce cancer. Additionally, the use of more sophisticated methods and minute exposures, with regard to hormone and neurological disruption, would be helpful in narrowing in on or a more useful assessment.

Leslie T. Stayner

Epidemiologic studies that provide quantitative exposure information for exposure-response analyses would be a high priority. Although it may be difficult to identify appropriate populations with well defined PCP exposures for study. An RfC could not be developed because of a lack of information from studies of inhalation to PCP. There is an obvious need for either toxicologic or epidemiologic studies to fill this gap. Mechanistic research that would support the development of a toxicokinetic model for route to route extrapolation would be highly desirable.

Paul B. Tchounwou

PCP is a systemic toxicant that has been reported to be carcinogenic from oral exposure studies; showing an increased incidence of non-Hodgkin's lymphoma and multiple myeloma in humans, and an induction of adrenal medullary and hepatocellular carcinomas, hemangiosarcomas and hemangiomas, nasal squamous cell carcinomas and mesotheliomas in rodents. However, the exact modes/mechanisms of action leading to carcinogenesis remain to be elucidated. Research is therefore needed to address this scientific gap. Microarray as well as differential display experiments will be useful in assessing the global gene expression associated with PCP exposure. Further molecular target evaluations will be critical to identify biomarkers and molecular pathways of PCP toxicity. Such studies would provide valuable information on the MOA, and would help in reducing uncertainty related to the low-dose risk estimation.

Although published studies have shown that PCP is well absorbed through all routes of exposures, limited information on its carcinogenicity via the inhalation and/or dermal

routes warrants further investigations. PBPD studies are also needed to describe the pharmacokinetics and pharmacodymanics of PCP toxicity.

Gary M. Williams

A study with aPCP to define dose response for BMD modeling.

DNA damage studies (comet or nucleotide postlabelling) in target organs of carcinogenicity

Comparison of quinone metabolites of PCP in dog liver nuclei relative to mouse and rat (Lin et al, 1997).

(A) General Charge Questions

4. Please comment on the identification and characterization of source of uncertainty in Sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Scott M. Bartell

The section on sources of uncertainty and their potential impacts is thoughtful and concise. For the most part, choices and assumptions are transparently and objectively described. However, some decisions could be described more fully. For example, the section on the LOAEL to NOAEL uncertainty factor (p. 147) describes the Mecler study findings and indicates that "a factor 3 was applied to account for the use of a LOAEL that is characterized by effects that can be considered mild at the POD," but no explanation is given for why the effects (chronic inflammation, increased liver weight, etc.) are considered to be mild.

The draft is somewhat vague regarding uncertainty in the low-dose extrapolation procedure. The table on p. 167 states that "departure from EPA's *Guidelines for Carcinogen Risk Assessment* POD paradigm, if justified, could ↓ or ↑ slope factor an unknown extent." Although the extent of change is generally unknown, it can determined for specific dose-response models. Because the multistage model has already been fit to the various data sets, it is relatively easy to determine the difference between slope factors estimated directly from the multistage model and slope factors estimated using the POD approach. Alternate dose-response models included in the BMDS package could also be fit with little difficulty, at least for the individual tumor sites. Such an exercise would help provide some quantitative information regarding the degree of uncertainty associated with the choice of low-dose extrapolation procedure, and could support the assertion (p.171) that there is "little if no difference" between the slope factors from the POD approach and the linearized multistage procedure used in the previous IRIS assessment.

Finally, the statement (p. 171) that "no additional uncertainty is added to the assessment by estimating combined risks reflecting multiple sites" is questionable. The assumptions used to derive Equation 2 in Appendix E-1 are not identified, but it appears that the carcinogenesis process is assumed to be completely independent across tumor sites. Whatever the assumptions used to derive this model, they should be clearly stated and discussed. In addition, the choice of prior distribution could be considered as a possible source of uncertainty in the combined analysis, as it may impact the resulting extra risk estimates.

Nasrin Begum

After reading and re-reading the review document, this reviewer believes most of the sources of uncertainty have been well identified and characterized. There are two sources of uncertainty that come to mind: (1) the length of the principal study, which correctly is less than chronic, being compared to other studies of extended duration, and (2) the extreme paucity of animals in any one dose tends to skew observed results, making the test less sensitive. A large number of the studies would be considered "ancient" and could be less sensitive than if they were run tomorrow. The choices and assumptions made in the discussion of uncertainty, as described, appear to be transparently and objectively presented. The impact of the uncertainties on the assessment has been adequately presented.

Leslie T. Stayner

For the most part, all of the sources of uncertainty were adequately discussed. For the cancer risk assessment, I think one source of uncertainty that should be further discussed is site concordance. The RA is based on liver, adrenal and circulatory system cancers, but lymphomas seems to be the most commonly reported association in the epidemiologic literature. It was also be highly useful to perform the cancer risk assessment using alternative models as a form of sensitivity analysis.

Paul B. Tchounwou

The identification and characterization of the source of uncertainty was done following standard protocols according to recommended guidelines. Specific considerations, related to PODs estimation and subsequent derivation of RfDs, were based on the most sensitive/critical effect (hepatotoxicity) observed in three different species. In addition PODs and RfDs were also developed for reproductive and developmental studies. Appropriate uncertainty factors related to interspecies, intraspecies, LOEAL to NOAEL extrapolations were used. The choices and assumptions were also appropriate and objectively discussed in light of the recommended guidelines for RfD development.

Gary M. Williams

Section 5.3 does not discuss uncertainty about whether effects of tPCP are due to aPCP.

Page 155 line 28: should discuss possibility that dogs may be more sensitive.

Chemical-Specific Charge Questions

(B) Oral reference dose (RfD) for Pentachlorophenol

1. A 1-year oral study in dogs by Mecler (1996) was selected as the basis for the RfD. Please comment on whether the selection of this study as the principal study is scientifically justified. Has this study been transparently and objectively described in the document? Are the criteria and rationale for this selection transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

Scott M. Bartell

The selection of the Mecler study is transparently and objectively described, and appears to be justified.

Nasrin Begum

This reviewer believes the use of the 1 year dog study is the appropriate study on which to base an RfD. The fact that the effects were essentially hepatotoxicity, and were also exhibited in every other species that was studied provides the rationale for choosing the effects in the dog. The results of this study and others indicating that the dog has the lowest LOAEL of those examined also provide criteria for the selection. These effects are quite objectively and transparently presented in the synopsis. It might be interesting to see the BMD of the other studies which had a NOAEL, albeit at higher doses, to see how the LOAEL with the extra 3UF compared with the BMD results.

Leslie T. Stayner

It seems the primary rationale for choosing the Mecler study over some of the other suitable studies is that its results identify effects at the lowest dose of any of the available studies. This is not a scientific choice but rather one that I believe is based on EPA risk assessment policy. However, it's not clear to me that this, in fact, is the study that yields the lowest RfD. In Figure 5-1, it appears that a lower RfD is derived from the study by Kimbrough and Linder (1978). However, in Table 5-1, use of the Mecler study appears to yield the lowest RfD. This discrepancy obviously needs to be resolved.

Paul B. Tchounwou

The selection of the 52-week repeated chronic oral dose study by Mecler (1996) as the principal study for RfD derivation was very appropriate, based on the fact that the resulting hepatotoxic effects were observed at the lowest tested dose of any of the published studies. This study was well designed and clearly showed dose-related increases in incidence and severity of hepatocellular pigmentation, cytoplasmic vacuolation, and chronic inflammation, and increases in liver weight and serum enzyme activity. The study is fully and objectively described (P 60-62).

Gary M. Williams

The study is well described, except that the nature of the pigment needs to be clarified. (LF is mentioned on page 142). Adequate scientific justification for Mecler (1996) as the principal study is provided in section 5.1.1.

No ADME in dogs.

(B) Oral reference dose (RfD) for Pentachlorophenol

2. An increase in hepatic effects (characterized by a dose-related increase in the incidence of hepatocellular pigmentation, cytoplasmic vacuolation, chronic inflammation, and severely discolored livers; statistically significant increases in absolute (females only) and relative liver weights, and serum enzyme activity) as reported by Mecler (1996) was selected as the critical effect for the RfD because these effects are considered by EPA to be indicative of hepatocellular injury. Please comment on whether the rationale for the selection of this critical effect is scientifically justified. Are the criteria and rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

Scott M. Bartell

The criteria and rationale for selecting hepatic effects to derive the RfD appears to be justified.

Nasrin Begum

After having read the various studies on the mechanism of action of PCP, it leaves little doubt that the exposure to PCP would be capable of producing hepatocellular injury. The effects reported for the uncoupling of oxidative phosphorylation, lipid peroxidation, GAP junction communication and cytotoxicity in several studies provide evidence that several of these effects could cause hepatocellular injury. This reviewer would have opted for a newer study with a lower dose to be tested. If more sensitive studies were to be completed, we would hope that the hormone and neurological evaluations would be most sensitive.

Leslie T. Stayner

Again, I have no problem with using the Mecler study or the subclinical hepatic effects seen in this study for the derivation of the RfD. However, if the RfD would be lower using a more serious outcome (liver necrosis) using the Kimbrough and Linder (1978) study, then it would seem more appropriate to use this study and endpoint for the derivation of the RfD.

Paul B. Tchounwou

The choice of hepatotoxicity as the critical endpoint is justified because the liver appears to be the primary target of PCP toxicity. Published research indicates that it is more sensitive to PCP toxicity than other tissues/organs.

Gary M. Williams

The rationale for selection of the critical effect is scientifically justified. Hepatotoxicity is a multispecies toxicity of PCP. The basis for selection is adequately described.

(B) Oral reference dose (RfD) for Pentachlorophenol

3. The hepatotoxic data and a NOAEL/LOAEL approach were used to derive the point of departure (POD) for the RfD. Please provide comments with regard to whether this is the best approach for determining the POD. Has it been transparently and objectively described? Please identify and provide rationales for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

Scott M. Bartell

Although BMD approaches are generally preferred to NAOEL/LOAEL based approaches, the report indicates that "application of BMD modeling was precluded based on a 100% response in animals for some of the hepatic effects, the small group sizes, and because the study did not test an exposure dose low enough to identify a NOAEL." This statement is confusing, because small group sizes and the lack of a NOAEL do not preclude dose-response modeling at all. To the contrary, BMD modeling has been advocated *because* it can be accomplished in absence of a NOAEL. Other studies have convincingly demonstrated that using fewer animals in more dose groups results in more precise BMD estimates than larger numbers of animals in few dose groups, so small group sizes *per se* are not a limiting factor. 100% response in some dose groups isn't necessarily a problem for dose-response modeling, though it can result in a relatively flat likelihood and difficulties in model fit, depending on the response levels in the other dose groups. In all, the argument presented for using the LOAEL instead of a BMD is unconvincing. If BMD modeling is attempted but fails to converge or yields implausible results, that would provide a convincing argument for reverting to the LOAEL.

Nasrin Begum

This reviewer does not believe that there is any better approach than the NOAEL/LOAEL, based on the studies and data that are available. The fact that the LOAEL does not lend itself to BMD modeling rather limits the use of the BMD method. This fact is quite clear and well presented in the document. There is one additional consideration that could be made concerning the BMD. If several of the other rodent studies did produce a NOAEL value at the lowest dose, it would be interesting to see if the POD produced provided something similar to the RfD determined with the LOAEL in the dog study. This would essentially support the RfD. However, the several rodent studies were of a shorter duration than that of the "chronic" dog study.

Leslie T. Stayner

It would obviously have been preferable to use a benchmark dose approach to derive the RfD. There were 3 dose groups in the Mecler study, so it should have in theory been possible to derive BMD. The document alludes to there being a problem to using this study for BMD modeling because "the data did not provide and adequate dose-response range for modeling" (pg 146). This is a little vague and it would be helpful if the

document presented a better explanation for why a BMD modeling approach was not feasible. It may also be possible to conduct BMD modeling with the Kimbrough and Linder study.

Paul B. Tchounwou

Published studies indicated that the hepatotoxicity POD was lower than that of reproductive and developmental toxicity. Hence, it is reasonable to expect that the corresponding hepatotoxicity RfD would also protect against reproductive and developmental effects. The use of the NOAEL/LOAEL approach for RfD derivation was appropriate.

Gary M. Williams

The selection of the LOAEL for the POD is adequately described.

(B) Oral reference dose (RfD) for Pentachlorophenol

4. The RfD is based on toxic effects observed in dogs (Mecler, 1996) administered a technical grade formulation of PCP (90.9% purity). Considering the toxicological database for PCP is largely comprised of studies that utilized similar formulations, as well as commercial and analytical (pure) formulations, please provide comments with regard to whether the use of data based on animal exposure to a technical grade PCP formulation of this purity is the best approach and can be considered representative of pure PCP. If not, please identify and provide the rationale for any alternative data sets, and the sufficiency of such data sets, to support derivation of the RfD.

Scott M. Bartell

The reasons for using the Mecler technical grade PCP study data have been transparently and objectively described. This approach appears to be well justified.

Nasrin Begum

This reviewer recognizes that several formulations of PCP were studied which varied in content, from about 90% to about 99%PCP. The data in the studies with different formulations did in fact exhibit a difference in severity mostly with the lower % PCP. These more toxic formulations were noted to contain some small percentages of furans, dioxins and or chlorophenols. Though the cleaner, analytic grade PCP produced less severe effects, we have to remember that in almost all cases, analytic grade PCP is too expensive to use in the commercial arena. As a consequence, the more contaminated, technical or commercial grade PCP is the chemical for which most if not all exposure occurs. Therefore, the use of the data from testing the technical or commercial PCP is the most appropriate for the determination of an RfD.

Leslie T. Stayner

The document makes a very good case for considering technical PCP to have the same toxicity as pure PCP.

Paul B. Tchounwou

Although analytical grade of PCP (aPCP) has a higher purity (98.6%), technical PCP (tPCP) formulation (90.6%) appears to be appropriate for RfD derivation. tPCP is the most commonly found formulation and is manufactured under several trade names including Dowicide 7, EC-7, Dow PCP DP-2, Duratox, Fungol, Penta-Kil and Permacide. It is therefore representative of PCP. The use of aPCP first requires a purification process to remove contaminants created during the production of tPCP. Most epidemiological studies relate human exposure to tPCP. Also, similar toxic effects have been reported from many studies comparing tPCP and aPCP toxicity. Moreover, hepatotoxicity, the critical endpoint, has been observed at similar or lower doses of tPCP than aPCP; meaning that tPCP-derived RfD would also protect aPCP-exposed populations.

Gary M. Williams

tPCP can be considered representative of aPCP.

(B) Oral reference dose (RfD) for Pentachlorophenol

5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the document? If changes to the uncertainty factors are proposed, please identify and provide a rationale(s). Please comment specifically on the following uncertainty factor:

- ***An uncertainty factor of 3 was applied in deriving the RfD to account for the use of a LOAEL rather than a NOAEL as the POD.***

Scott M. Bartell

Although most of the choices for the uncertainty factors are consistent with previous risk assessments, the choice of 3 for the LOAEL to NOAEL uncertainty factor is somewhat surprising. The hepatic effects (chronic inflammation, increased liver size, etc.) in the Mecler study seem fairly serious, but are described as "mild" in justification a factor of 3 rather than a more typical factor of 10. Moreover, because dosing occurred over only 1 year in a species with a longer lifespan, it seems likely that some of the milder hepatic effects would have been more severe with an extended duration of dosing.

Nasrin Begum

The use of the different UFs (10 x 10) has been used in the Agency for about 39 years. It has been well established over the many years of use and accepted virtually world wide. However, the UF of 3 for use on a LOAEL is quite a different story. It was first brought forth in the mid-1980s. Not all people wanted to use it, and the derivation should be briefly mentioned in order for a more comfortable feeling with the RfD.

Leslie T. Stayner

As far as I know, a factor of 10 has been traditionally used to account for the use of a LOAEL rather than a NOAEL. The justification given for this departure is that the endpoint being used is subclinical. This is of course a policy call, and I am not sure if EPA policy clearly lists this as an option. Scientifically, I don't see why the relationship between a LOAEL and a NOAEL would differ for subclinical and more serious clinical effects.

Paul B. Tchounwou

The hepatotoxic effects (pigmentation, chronic inflammation, cytoplasmic vacuolization, hepatomegaly, and increased ALA and ALP activity) observed at the LOAEL were mild. Although a higher value (5) of uncertainty factor (UF) would have provided a more stringent RfD, the use of an UF of 3 to account for the use of LOAEL instead of the NOAEL was appropriate.

Gary M. Williams

An uncertainty factor of 3 was applied in deriving the RfD to account for the use of a LOAEL rather than a NOAEL as the POD. Page 155 Line 22 gives a different rationale. Based on effects over the dose range, 3 is reasonable.

(C) Inhalation reference concentration (RfC) for Pentachlorophenol

1. An RfC was not derived due to the lack of available studies to characterize the health effects associated with pentachlorophenol administered via the inhalation route. Are there available data that might support development of an RfC for pentachlorophenol?

Scott M. Bartell

I am not aware of any such data.

Nasrin Begum

The absence of an RfC derived from chronic data is obvious. However, the Agency does have access to Task Force which does establish short-term RfC values. The several studies presented in synopsis form do indicate that there are some data which might be useful to the Task Force, but would not fulfill the normal need of data to produce an RfC.

Leslie T. Stayner

I am unaware of any data to allow the direct computation of an RfC.

Paul B. Tchounwou

It was not possible to derive an RfC because no chronic studies on inhalation exposure to PCP have been published or made available.

Gary M. Williams

Not to my knowledge

D) Carcinogenicity of Pentachlorophenol

1. Under EPA's 2005 "Guidelines for Carcinogen Risk Assessment" (www.epa.gov/iris/backgr-d.htm), the Agency concluded that pentachlorophenol is "likely to be carcinogenic" to humans. Please comment on the cancer weight of evidence characterization. Has the scientific justification for the weight of evidence descriptor been sufficiently, transparently and objectively described? Do the available data for liver, adrenal gland, and circulatory system tumors in mice and nasal tumors and mesotheliomas in rats support the conclusion that PCP is a likely human carcinogen?

Scott M. Bartell

This characterization of the weight of evidence appears to be consistent with the 2005 guidelines, but the reasoning is not discussed extensively. It would appear that the evidence for carcinogenicity is quite strong for animals and reasonably strong for observational studies in humans, but that the lack of understanding of mode of action and identified precursors in humans precludes classifying PCP as "carcinogenic to humans." The rationale for selecting "likely to be carcinogenic" instead of other categorizations should be explicitly stated.

Nasrin Begum

This reviewer believes that the scientific justification of the weight of evidence descriptor has been sufficiently transparent and objectively described. The weight of evidence, however, encompasses more than just tumor occurrences in two species here. The tumors appear to be significantly increased in male rats and both sexes of mice. The other weights include strong evidence in human epidemiologic studies indicating increased risks of lymphoma, multiple myeloma, and soft tissue sarcoma, and only limited evidence of liver cancer associated with PCP exposure. Recent studies have found positive evidence of hepatocellular tumor promoting activity, and lymphoma and skin-adenoma promoting activity in mice. With this added information, it is difficult to deny the Agency's conclusions concerning the likelihood of being carcinogenic to humans.

Leslie T. Stayner

Given the evidence, the classification of likely seems appropriate. An excess of lymphomas has been observed in numerous investigations of workers exposed to PCP. The strongest evidence comes from a recent study of saw mill workers in British Columbia, which reported strong evidence of an exposure-response relationship for PCP and NHL (Demers et al. Cancer Causes Control (2006) 17:749–758). Further support comes from a new NIOSH study that was not included in the review, which is going to be presented at a conference this summer (Ruder and Sweeney 2009). The study, which is based on a NIOSH cohort of PCP production workers, has also observed an association between NHL and exposure to PCP (17 deaths, SMR 1.76, CI 1.02-2.82). Thus based on

the epidemiologic evidence alone I think that the weight of evidence is sufficient to classify PCP as being likely to cause cancers in humans. The fact that an increased incidence of cancer has been observed in several animal species further supports this determination.

Paul B. Tchounwou

The conclusion that pentachlorophenol is likely to be carcinogenic to humans is very appropriate, based on the EPA "Guidelines for Carcinogen Risk Assessment." Although there is no convincing evidence from epidemiological studies that PCP produces/induces human cancers, there is sufficient evidence from well designed experimental studies showing a strong association between PCP exposure and induction of several neoplasms including hepatocellular adenomas and carcinomas, adrenal medullary pheochromocytomas, hemangiomas and hemagiosarcomas, and nasal squamous cell carcinomas and mesotheliomas. There is also strong evidence from epidemiological studies that PCP exposure increases the risk on non-Hodgkin lymphomas and multiple myelomas, some evidence of soft tissue sarcomas, and limited evidence of hepatocellular carcinomas. In agreement with EPA, the International Agency for Research on Cancer categorizes PCP in Group 2B, meaning that it is possibly carcinogenic to humans.

Gary M. Williams

In the absence of a MOA of established relevance to humans, the animal tumor findings only support "possibly" carcinogenic to humans. I cannot locate the WOE descriptor.

D) Carcinogenicity of Pentachlorophenol

2. A quantitative oral cancer assessment has been derived for PCP. Do the data support an estimation of a cancer slope factor for PCP? Please comment on the scientific justification for deriving a quantitative cancer assessment. Has the rationale and scientific justification for quantitation been transparently and objectively described?

Scott M. Bartell

The data clearly support the estimation of a cancer slope factor.

Nasrin Begum

This reviewer believes that the data in the mouse NTP study support an estimation of a cancer slope factor for PCP. In the present case, since the MOA is not clear cut in determining the method of cancer production, it was wise to follow the agency Cancer Assessment Guideline 2005. A BMD was calculated to use the best fit of the multistage linear extrapolation. Rationale for the use of these models and methods for quantitation are both objectively and very transparently described in the document.

Leslie T. Stayner

I do believe that there is adequate data for the estimation of a cancer slope factor for PCP. The rationale and scientific justification for the derivation of the slope factor are well described and justified. The use of a linearized multistage model is appropriate given that there is not sufficient information to develop a more mechanistic model. Linear extrapolation of the risk from this model is appropriate and consistent with EPA guidelines for when we don't know enough about the MOA to challenge this assumption. As mentioned earlier, it would be useful to evaluate the uncertainty related to this modeling approach by performing sensitivity analyses using alternative models.

Paul B. Tchounwou

The estimation of the cancer slope factor was based on the integration of specific risk data with corresponding BMDs, using the low-dose linear extrapolation approach to describe the cancer risk per unit dose of PCP at low doses. The linearized multistage model was applied due to the lack of scientific information on PCP MOA. The scientific data used for estimating the cancer slope factor were appropriate.

Gary M. Williams

Derivation of a quantitative cancer assessment is justified. The rationale and methods are adequately described.

D) Carcinogenicity of Pentachlorophenol

3. A two-year oral cancer bioassay (NTP, 1989) in mice was selected as the principal study for the development of an oral slope factor. Please comment on the appropriateness of the selection of the principal study. Has the rationale for this choice been transparently and objectively described?

Scott M. Bartell

The NTP bioassay appears to be an appropriate choice.

Nasrin Begum

This reviewer sees that the selection of the principal study was chosen due to the multiple tumor sites in the animals. This gives the study author the ability to add the individual quantitations and produce a cancer slope factor that is a worst case situation. By using this method of multiple tumor sites, the authors were able to essentially strip away the single cancer slope factor of a single site and show significance of the added contaminants. The presentation of the development of the slope factor rationale was very well presented, with objectivity and good transparency.

Leslie T. Stayner

It is unfortunate that there are no human data that could be used to derive the slope factor, but that is not something that EPA can solve at least in the short term. The NTP study in mice does appear to be the best data available for the development of a slope factor.

Paul B. Tchounwou

The selection of the NTP's two-year oral cancer assessment as the principal study was very appropriate. This was a well-thought out and carefully designed and executed study that resulted in an increased incidence of hepatocellular adenomas and carcinomas, benign and malignant adrenal medullary tumors, and hemangiomas and hemagiosarcomas in PCP-exposed mice; making it possible to calculate the slope factor based on the integration of tumor incidences at multiple sites.

Gary M. Williams

Mouse liver carcinogenicity is species specific, i.e. rat not affected, and hence justification for its use should be provided. Also, since the MOA involves a promoting action of PCP, the possibility of a threshold should be considered.

D) Carcinogenicity of Pentachlorophenol

4. Data on the mode of action (MOA) of carcinogenicity of PCP was considered. Several hypothesized MOAs were evaluated within the Toxicological Review and EPA reached the conclusion that a MOA(s) could not be supported for any tumor types observed in animal models. Please comment on whether the weight of the scientific evidence supports this conclusion. Please comment on whether the rationale for this conclusion has been transparently and objectively described. Please comment on data available for PCP that may provide significant biological support for a MOA beyond what has been described in the Toxicological Review.

Scott M. Bartell

This conclusion appears to be supported by the weight of scientific evidence.

Nasrin Begum

This reviewer notes that the scientific evidence has provided several metabolites which, in their own right, may be possible of transforming cellular organelles to the point of producing a tumor cell. However, in no case did the individual studies show that a particular metabolite produces tumors through any pathway. Therefore, the weight of evidence does support the conclusion that a MOA or several MOAs could not be supported for any particular tumor types observed in animal models.

Leslie T. Stayner

I am not an expert on this, but I was convinced by EPA's argument that a MOA could not be established at this time. In fact, it seems likely that there may be several MOAs, some of which would clearly be expected to be consistent with a low dose linear dose-response assumption.

Paul B. Tchounwou

Chronic exposures to PCP resulted in an increase of selected tumors in epidemiological studies, or an induction of many types of neoplasms in experimental studies. However, the exact mechanisms of PCP-induced tumorigenesis were not clearly elucidated. Although few studies have looked at the role of ROS in PCP toxicity, further studies are needed to investigate the cellular and molecular events leading to cancer formation in PCP-exposed animals.

Gary M. Williams

The available data for consideration of a MOA were not adequately discussed.

The findings of mouse liver tumor promotion and lack of initiation (Section 4.2.4.1.1) were not considered.

Page 133, Line 7….what is the evidence for this statement?

Page 135, Line 16…why is the oxidative DNA damage data "limited?" It has been reported in several independent studies.

No discussion of why rat liver not a target. Lin et al (1977) reported that mice had a four-fold greater dose of quinone metabolites to liver nuclei than rats.

D) Carcinogenicity of Pentachlorophenol

5. Increased incidence of tumors in male and female B6C3F$_1$ mice was observed following administration of two formulations of PCP (technical grade PCP and EC-7 [a commercial grade of PCP]) that contain various chlorophenol and chlorinated dibenzodioxin and dibenzofuran contaminants. The carcinogenic contributions of PCP versus those of contaminants have been described qualitatively and to a limited extent quantitatively within the document. The cancer assessment is based on the data sets resulting from exposure to two different formulations that are approximately 90% PCP, with the assumption that carcinogenic contributions from the contaminants are minimal. Please comment on the scientific justification and transparency of this analysis. Please comment on whether these are the appropriate data sets on which to base the cancer risk estimate and, if not, please identify and provide the rationale for any alternative data sets, and the sufficiency of such data sets, to support estimation of cancer risk.

Scott M. Bartell

The analysis is generally transparent and justified. However, it is not at all clear why the data for technical grade PCP formulation was chosen over the EC-7 formulation for characterizing PCP risks. The brief paragraph on p. 166 does not offer a strong argument for choosing tPCP over EC-7. For example, it is asserted in that paragraph that "the assumption that TCP minimally contributes to the estimated cancer risk for EC-7 indicates that the oral slope factor of 2×10^{-1} (mg/kg-day)$^{-1}$ underestimates the risk associated with aPCP." Although the stated assumption does suggest that the slope factor for EC-7 is an underestimate of the slope factor for aPCP, the same reasoning applies equally to tPCP.

It is entirely possible that the differences in slope factors for tPCP and EC-7 are due to random variability in the experimental responses, rather than some difference in the carcinogenicity of the underlying formulations. This view is supported by the fairly similar BMDs (not the BMDLs, which are more sensitive to sample size) for tPCP and EC-7. Because the two formulations have similar PCP content and the carcinogenicity for both is thought to be attributable only to PCP, one approach that should be considered is to pool the tPCP and EC-7 data sets with the same outcome.

In addition, the approach described on p. 165 for rescaling the slope factors by 1/purity appears to be justified, as the other known constituents are unlikely to contribute substantially to the carcinogenicity of tPCP (as discussed on pp. 165-166). However, it does not appear that the purity rescaling factor was applied in the estimation of the slope factor for aPCP.

Nasrin Begum

Based on the write-up, this reviewer believes that, in following with the EPA Cancer Risk Assessment Guidelines (2005), the results are a reasonable estimation method of the

contaminant contribution of cancer risk. These data provide the most sensitive risk assessment. The only other chronic study on PCP is a 2 year rat study. It produced nasal and mesothelioma tumors at reasonably high doses. The nasal tumors may have been due to an exquisite type of nasal cell able to preferentially metabolize PCP better than other cells. This reviewer would not feel safe invoking this study as a significant set of data, sufficient enough to estimate the cancer risk. Since there is no known or proven MOA for a particular tumor type, it would be best to take the most sensitive risk value, as appropriate.

Leslie T. Stayner

I found EPA's argument convincing that the contribution of the contaminants to the carcinogenic response observed in these studies would be minimal. Given this assumption it may make sense to pool the findings from the NTP study for tPCP with EC-7 if these studies do not have significantly different results.

Paul B. Tchounwou

I concur with EPA assumption of the minimal carcinogenic contribution of chemical contaminants in PCP carcinogenesis. NTP reported that tPCP contains about 90% PCP, 4% TCP, 6% chlorohydroxydiphenyl esters and trace amounts of chlorinated dibenzodioxins and dibenzofurans, while EC-7 contains about 91% PCP and 9% TCP. It was estimated that the calculated slope factor of 0.4 / mg/kg-d for tPCP was associated with the combined cancer risk for tPCP and its contaminants. However, limited information is available regarding the carcinogenic potential of each of the impurities. Although TCP, the most common contaminant of tPCP and EC-7 showed some evidence of carcinogenicity, the available data did not allow for a quantitative assessment. Also, in light of other contaminants present, risk estimates were mostly attributed to the whole tPCP and EC-7 formulations including the impurities.

Gary M. Williams

It is a reasonable assumption that the effects of tPCP are due to aPCP. However, it is only an assumption. The mouse liver promotion study of Umemura et al (1999) was done with aPCP and supports the interpretation that the liver effects are due to aPCP.

D) Carcinogenicity of Pentachlorophenol

6. Data on tumors in the liver and adrenal gland in B6C3F$_1$ male mice administered technical PCP were used to estimate the oral cancer slope factor. Please comment on the estimation of a statistically appropriate upper bound on total risk (combined slope factor), which describes the risk of developing any combination of tumor types considered. Please comment on the scientific justification and transparency of the analysis for combining these data to derive the oral cancer slope factor. Please comment on the use of data in male mice exposed to technical PCP for a cancer risk estimate for both technical and analytical PCP.

Scott M. Bartell

The combined analysis is justified, but the particular choice of bootstrap technique may not be ideal. The modification of empirical response probabilities using the uniform Bayesian prior may influence the slope factor. If the slope factor is invariant to the prior, that should be demonstrated with a prior sensitivity analysis. If not, the choice of prior should be justified.

Was a parametric bootstrap considered? Why not use the Equation 2 model and parameter estimates from the primary data sets in order to directly characterize the binomial response probabilities at each dose in the experimental study, and then simulate the binomial responses from those probabilities and the number of animals tested at each dose? Such an approach would avoid the need for a Bayesian prior, as the fit probabilities would never be exactly 0 or 1. Moreover, the confidence limits from the parametric bootstrap would more clearly be comparable to the confidence limits generated by BMDS.

Nasrin Begum

Considering that time to tumor modeling and survival issues were not expected to impact the dose response relationship, incidence data were censored accordingly. Statistical analysis was checked by the reviewer, and it is found that there is no difference present in proportion of responders for hepatocellular adenoma/carcinoma or adrenal benign/malignant pheochromocytoma between the treated and control groups. Because of this reason, a dose-response analysis for tPCP and EC-7 conducted using combined control group is supposed to be scientifically justified. Since the incidence data, chi-square test result and Fisher exact test were presented in the report, this reviewer had a chance to check the analyses, which indicate it was transparent (Table 5-5 and D-1) and clearly stated.

Leslie T. Stayner

The method for combining the risk estimates across the cancer sites was innovative and appropriate if one can assume these sites are independent. If possible it would be desirable to test this assumption of independence by further analysis of the NTP database.

Paul B. Tchounwou

Male B6C3F1 mice were used to estimate the oral cancer slope factor, based on the findings that the males were consistently more sensitive than the females to PCP tumor-induction. In accordance with the NCR guidelines, an estimation approach based on the combination of risk estimates from separate tumor sites is recommended. The estimated 95% upper confidence limit was about 38% higher than the 0.29/mg/kg-d cancer slope factor computed for liver tumors in tPCP exposed mice only. Hence, combining the risk estimates for any combination of tumor sites provided a more reasonable and conservative approach. Also, the risk estimates for tPCP tend to be higher than those for EC-7; indicating greater potency for tPCP.

Gary M. Williams

Use of data with tPCP involves uncertainties, which are discussed.

V. SPECIFIC OBSERVATIONS

Scott M. Bartell

p. 7, what does "CD" stand for in "Charles River CD rat?"

p. 20, why omit small cohorts from the discussion? It may make sense to exclude on the basis of studies lacking methods descriptions, but it is odd to exclude on basis of a small sample size, given the inclusion of case reports (n=1) and many small toxicology studies. It might be better to report information from these studies but indicate reasons why they should be discounted.

p. 20: should be "durations… were" or "duration… was"

Table 4-1 would be more interesting if it listed the actual effect sizes rather than just indicating what effects were statistically significant.

p. 22: it is unclear whether or not these SMRs are adjusted for exposures to other chemicals.

p. 23, correlation coefficients of 0.76 and 0.72 are not entirely convincing in the way of validation

On p. 26 it is stated that "It is difficult to conceive of a way in which the observed associations could be explained by confounding." This is rarely, if ever, true for epidemiologic studies. Have other occupational exposures been fully addressed? What about residual confounding by inadequate control for age or other variables?

p. 30, an odds ratio of 0.65 could indicate an association, albeit a protective effect.

p. 31, "The measure of association, based on the conditional logistic regression analysis of the matched triad data for PCP was not presented." Was the statistical significance reported, at least?

p. 32, "Population-based controls were drawn using a randomization scheme based on personal identification numbers, and were matched to the age and sex distribution of the cases." Was this really frequency matching, as implied by this wording, or individual matching?

p. 33: unclear who provided the information on parental exposures for older children.

p. 33, "the exposure assessment methodology used in case-control studies can result in useful between-group comparisons of risk if the intra-group variability is less than the inter-group variability in potential exposure levels." The reasoning behind this statement is unclear; please elaborate or provide citations. Is this really an issue that pertains to case-control design, or is it retrospective or JEM based exposure assessment?

p. 36, "A limitation of these studies is the relatively large proportion of proxy respondents used (cases and matched controls), which is likely to result in a loss of precision and possible attenuation of the observed association." Isn't (differential) recall bias a more significant threat to the validity of these studies?

p. 40, "An increased prevalence (trend $p \leq 0.05$) of weight loss, fevers, excess fatigue, upper respiratory tract symptoms, history of emphysema or bronchitis, and current or history of nausea was seen in the high-exposure group." Was the trend test conducted across the three exposure groups, or across individuals within the high-exposure group? Unclear from this wording.

p. 141, "Many of the pertinent animal studies have provided evidence that it is not the parent compound itself but hydroquinone and benzoquinone metabolites of PCP that are the biologically reactive intermediates. This implies that metabolism is required for toxicity to occur." This is a very critical point, and explains the rationale for not attempting to extrapolate across exposure routes without a good understanding of the toxicokinetics including metabolism.

How were the time-averaged body weights calculated (p. 161)? Did they only include adult weights, corresponding with the 70 kg human body weight estimate? How many weight measurements were taken per animal?

p. 164, "formulation" should be "formulations."

p. 165, "6 × 103" appears to be a typo, meant to be in scientific notation…

p. 172 includes a long paragraph describing cancer outcomes, but is listed under a "Noncancer" heading.

Survivorship appears to be quite low in the NTP data (p. D-2). Although the approach taken to exclude early deaths from the denominators is not unreasonable, it is clearly *ad hoc* and not the only approach that could be used. There are formal censored data analysis methods (such as life tables, Kaplan-Meier estimates, and parametric survival analysis) available for such data; these should be considered as alternatives.

Was 1% or 10% used as the benchmark response level in the combined analysis? 1% is indicated on p. 246, but other text suggests 10%.

Nasrin Begum

The following list of words and suggestions are provided as possible changes that may be or not an improvement to the draft.

Page	Page/247 [Word]	Line	Comment
	21/247		The semi log plot showed. If it shows, then where is it?
	21/247	Par. 2	Add the word the following the
	21/247		The abbreviation T2 is not in the list of abbreviations on page 11.
	21/247	Par. 7	After the number 1.13%, add "of the dose."
8			Add the word "routes."
8			Add the word bioavailability "was."
8			Absorption, add the word "kinetics"…of 14C
14		5	Make "minutes" singular.
14		7	The word should be minute.
14		10	Replace "exhibited" with "found."
14		16	End the sentence with male and female, using 2 dosages.
14		17	The sentence is too long.
14		23	Add "test material" after "…37-41 mg/Kg…"
14		31	Add the word "an" following the word "after."
14		33	The quantities, 5 and 24% TCHQ are not approximately the same amount.
15		1	Is this line supposed to be a sentence?
15		5	Isn't this supposed to be "micrograms/hr/mL?"
15		7	Add the % sign after the number 31.
15		8-9	Braun (1977), above, does not provide for a comparison here.
16		21	It seems that the sentence is backwards, and may read better with the verbiage first, then the signs ->.
17		7	Add the words "urinary levels."
17		13	Add the item "[14C]PCP" in acetone.
17		28	Add the word "into" before the word "mice."
17		29	Place the word "the" before the word "mice."
17		17-18	Delineate the dose system, if it's [14C] or not.
17		21-25	Is this the reviewer's conclusions, or those stated in Bevenue (1967)?
21			Exposure Assessment: dioxinsb? Shouldn't this be a superscript?
23		8	Add the word "the."
26		19	Change to "…except by confounding…"
30	44/247	32	This is not clear with regard to how continuous (1 mo.) of virtually no exposure equals high exposure.
32		32	Does this mean in a sawmill, or as timber?

33		22-27	This is too long of a sentence.
33		30	After the word “rare,” add “tumors.”
33		32	After the word “specific,” add “exposure.”
34		29-30	Do we really need commas here?
35		3	By reversing the levels and comparisons, could be made clearer.
35		32	Remove the “s” from “cancers” and add the word “alternatively.”
36		4	Change “sawmills” to “sawmill.”
36		18	Change “Demer” to “Demers.”
36		35	Add an “a” after the word “only.”
78	92/247	33	LOAEL = 30, based on the paragraph.
78	92/247	36	NOAEL = 10, based on paragraph. Delete “could not.”
85		22	Change to in “only” the 15 mg.
86		11	As 2% in H2O?
96	110/247	33, 35	Add “of.”
97	111/247	24, 25	How can you say “it induced” when it's not considered statistically significant?
98	112/247	8	Replace “exhibited” with “found.”
100	114/247		Doses would help!
101	115/247	10	Replace “with” with “at.”
102	116/247	2	Was the increase statistically significant?
102	116/247	10	Replace “are” with “were.”
103		6	Delete “to PCP.”
104		25	Delete “the.”
104		28	Change “amounts” to “occurrences.”
105		37	Insert “values were estimated and extracted.”
106		14	What is ROS?
106		21	What is SOD
108		16	Is this 50 µg TCPHQ?
150	164/247	Table 5-1	The value for Kimbro is 0.002, not 0.02.
157		21	Should it be “less than (or)?"
157		35	Delete “…and monthly for.”
158		26	Basis size: Where is this reported and by whom?
	159/247	27, 28	Did you mean Toxic effects were NOT?
168	182/247	35	Remove “monthly.”
168		34	Add “that.”
170		2	Substitute the word “estimated” for the word “considering.”
170		15	Add the word “in” after the word “are.”
170		26	Substitute the word “in” for the start of Regs…..extrapolation.
170		31	By using the wording, “With respect…,” you give it a very weak start!
172	186/247	23, 27- 35	This belongs in the cancer section.

221/247	Part 2	(title)…spell out the word "pheochromocytoma."
227/247	Part 4	
239/247	Part 8	

Leslie T. Stayner

I have the following additional comments:

1. Page 22, lines 22-23: The exposure assessment in this study is both a strength and weakness. It should be noted that the exposure rating was qualitative, which is a big limitation for the purposes of quantitative risk assessment.

2. Page 26, lines 29-31: The correlation is not that low that I can assume that the association with PCP would not be attenuated if it was controlled for TCP. I would think it would be possible to request that the authors perform this analysis.

3. Page 27, line 10: Another limitation is that there was co-exposure to formaldehyde. There is evidence that exposure to formaldehyde may be associated with an increased risk of hematic and lymphatic neoplasm's.

4. Page 22, line 16 and elsewhere in the document: The document appears to confuse analysis of latency with using a lag period. They are not exactly the same thing although closely related. Lag involves ignoring exposures received within some period of time prior to the evaluation of risk. The assumption is that exposure during this period of time is irrelevant. A latency analysis treats study subjects as non-exposed until a certain period of time after their first exposure. The analyses presented in the Demers paper are lag and not latency analyses. I strongly suspect that what are described as latency analyses for the other epidemiologic studies reviewed are also lag analyses, but these needs to be checked.

5. Page 34, lines 12-13: The study by Kogevinas also involved internal comparisons.

6. Page 35, last para: It should be noted that an excess of liver cancer has not been reported in any of the other cohort studies.

7. Page 36, line 28

References:

Mannetje A, McLean D, Cheng S, Boffetta P, Colin D, Pearce N. (2005) Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. Occup EnvironMed62:34–40

McLean D, Eng A, Dryson E, Walls C, Harding E, Wong KC, Cheng S, Mannetje A, Ellison-Loschmann L, Slater T, Shoemack P, Pearce N. (2009) Morbidity in former

sawmill workers exposed to pentachlorophenol (PCP): a cross-sectional study in New Zealand. Am J Ind Med. 2009 Apr: 52(4):271-81.

Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, Gnepp DR, Brann EA. (2000) Occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. Am J Ind Med 37:532–541

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Page iii, Line 3…Replace "INFORMATION" by "PROPERTIES."

Page x…Add and define MLE (see table on Page 167), and UCL (upper concentration limit).

Page 2…It would be better to present the physical and chemical properties of PCP in form of a table.

Page 4, Line 8…Delete "s" from "indicates."

Page 62, Line 20…Add "exposed to tPCP" to the title of the table.

Page 85, Line 19…Delete "/doe."

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Page 9: Section 3.2.1.3: Metabolism should be subdivided into sections for human, animal and subcellular.

Page 13: Fig 3 goes beyond metabolism to include effects on DNA, presuming that TCpHQ and TCoBQ react with DNA. Fig 3 needs a legend. TCHQ and TCoHQ are not shown in Figure 3.

Page 96: Section 4.5: There is no discussion of promotion. No conclusion.

Page 104: Bodell and Pathak (1998) is only an abstract.

Page 105: Section 4.5.3: Lin et al. (1997) also studied protein adducts.

Page 156, Line 23: What was the mode of administration?

Page 168 line 23: Changes in oxidative stress in human tumors are not relevant to pathogenesis of PCP-induced neoplasms.