**Draft Charge to External Reviewers for the IRIS Toxicological Review of
Pentachlorophenol
April, 2009**

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.