Proposed Listing of Pentachlorophenol (PCP) for Inclusion in 13th Report on Carcinogens (RoC)

Submitted on Behalf of the Pentachlorophenol Task Force

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I. Introduction

A recent notice in the Federal Register (FR) [Vol. 77 (12), Jan. 19, 2012] requested public comments on a number of substances under consideration by the National Toxicology Program (NTP) for inclusion in the next (i.e., 13th) Report on Carcinogens (RoC). Pentachlorophenol (PCP) was one of the chemicals listed in the FR notice. According to the guidelines of the Office of the RoC, "*...information about published, ongoing, or planned studies related to evaluating carcinogenicity*" as well as "*...scientific issues important for assessing carcinogenicity of the substance*" are the ultimate basis for reaching a listing decision concerning any particular chemical.

As part of the listing process, the NTP prepares a draft background document for each candidate substance under consideration. While this has not yet been done for any of the chemicals proposed for listing, each chemical-specific document includes consideration of a key relevant element, i.e., *Human Exposure.* Because exposure (typically occupational) to PCP is often confounded by simultaneous exposure to other chemicals (i.e., chlorophenols other than PCP, dioxins, phenoxy herbicides, etc) for purposes of a potential RoC listing, primary emphasis must be placed on those studies that are capable of isolating exposure to PCP alone. This means that studies which report associations between exposures to "chlorophenols" without an ability to designate specific exposure to PCP cannot be relied upon since it would be disingenuous to base a RoC listing of the potential carcinogenicity of PCP (CAS# 87-86-5) on studies where co-exposures to another IARC-listed chemical (i.e., dioxin, phenoxy herbicides) could have played a contributory role in the reported results. This would particularly be the case for dioxin (i.e., 2,3,7,8-TCDD) which is listed in the RoC as a known human carcinogen. Since the FR notice is quite explicit that only PCP is under consideration for potential listing in the RoC, it would be inappropriate to rely on studies where co-exposures to other chemicals cannot be ruled out as potential contributors to reported effects.

Since the process leading up to the 13th RoC is at the beginning stages there is no NTP background report on PCP to critique. Consequently, since the latest authoritative review of PCP is the IRIS (2009) assessment of PCP this document (in addition to Collins et al. 2009 and Ruder and Yiin 2011) will provide the basis for the present comments recognizing that the IRIS (2009) review falls short of an unbiased assessment as documented in previous comments by the Pentachlorophenol Task Force to the IRIS docket. Given the importance of this issue, it is also assumed that the NTP, as part of the RoC process, would be more inclined to conduct evidence-based assessments in a manner that avoided the kinds of generic problems identified by the National Academy of Sciences (NAS 2011) panel which reviewed the IRIS (2010) assessment of formaldehyde. These included "*Strengthened, more integrative, and more*

transparent discussions of weight of evidence are needed. The discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence, such as consistency." This suggests that if the IRIS (2009) PCP assessment was not conducted in the spirit of the recent NAS recommendations that the studies selected as the basis for establishing causality for PCP carcinogenicity were those most likely to support this conclusion.

The *Toxicological Review of Pentachlorophenol* prepared by the National Center for Environmental Assessment (NCEA) for the Integrated Risk Information System (IRIS) includes the following summary statement concerning the overall weight of evidence for PCP carcinogenicity:

> *Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), PCP is likely to be carcinogenic to humans by all routes of exposure. This cancer weight of evidence determination is based on (1) evidence of carcinogenicity from oral studies in male mice exhibiting hepatocellular adenomas and carcinomas, pheochromocytomas and malignant pheochromocytomas; and female mice exhibiting hepatocellular adenomas and carcinomas, pheochromocytomas and malignant pheochromocytomas, and hemangiomas and hemangiosarcomas (NTP, 1989); (2) some evidence of carcinogenicity from oral studies in male rats exhibiting malignant mesotheliomas and nasal squamous cell carcinomas (Chhabra et al., 1999; NTP, 1999); (3)* ***strong evidence*** *from human epidemiologic studies showing increased risks of non-Hodgkin's lymphoma and multiple myeloma,* ***some evidence*** *of soft tissue sarcoma, and* ***limited evidence*** *of liver cancer associated with PCP exposure (Demers et al., 2006; Hardell et al., 1995, 1994; Kogevinas et al., 1995); and (4) positive evidence of hepatocellular tumor-promoting activity (Umemura et al., 2003a, b, 1999) and lymphoma and skin-adenoma promoting activity in mice (Chang et al., 2003).* [emphasis added]

Subsequent to the IRIS (2009) review Collins et al. (2009) and Ruder and Yiin (2011) published the results of other relevant studies, which, in conjunction with the four studies noted will be considered as the most appropriate basis for a weight of evidence evaluation of the available data concerning the potential carcinogenicity of PCP in humans. Since these six studies are assumed to be the most relevant (many are follow-ups of previous studies) the remainder of this comment will focus on these studies as the most appropriate basis for assessing the weight of evidence (WOE) for potential PCP carcinogenicity in humans. This pertains to whether these six studies support an evidence-based conclusion that there is **strong evidence** that PCP is a cause of non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM), **some evidence** for soft tissue sarcoma (STS) and **limited evidence** for liver cancer. Each of these evidence categories must be explicitly fulfilled by PCP itself without confounding by co-exposures to any other chemicals.

The EPA (2005) *Guidelines for Carcinogen Risk Assessment* ("*Guidelines*") provide a number of explicit recommendations and criteria for evaluating a body of literature in order to establish whether a particular chemical might be carcinogenic to humans. The *Guidelines* unequivocally endorse the use of a weight of the evidence (WOE) approach when evaluating the epidemiological data on a particular chemical. Some key highlights from these guidelines should be noted. In discussing the assessment of evidence of carcinogenicity from human data EPA (2005) states:"***All studies that are considered to be of acceptable quality****, whether yielding positive or null results, or even suggesting protective carcinogenic effects, should be considered in assessing the totality of the human evidence. Conclusions about the overall evidence for carcinogenicity from available studies in humans should be summarized along with a discussion of uncertainties and gaps in knowledge."* [emphasis added] Further, the *Guidelines*

suggest that *"The general evaluation of the strength of the epidemiological evidence reflects consideration not only of the magnitude of reported effects estimates and their* ***statistical significance****, but also of the* ***precision of the effects estimates and the robustness of the effects associations.****"* [emphasis added] The highlighted points are emphasized since, as discussed below, many of the associations between exposure to PCP and the various cancers of concern are not statistically significant. Additionally, the *Guidelines* are quite explicit that the following *"causal criteria…should be used to determine the strength of the evidence for concluding causality"* including the consistency, strength, specificity and temporal relationship of the observed association, the biological gradient (exposure-response relationship), biological plausibility and coherence. While it is unknown if NTP (and therefore the RoC) is bound by EPA guidelines in preparing RoC listing assessments, if this is not the case, it is incumbent that the explicit criteria by which evidence is evaluated be clearly stated.

II. Review of Six Key Epidemiology Studies on PCP

As noted above, the overall conclusions from the IRIS (2009) assessment state that there was *"strong evidence from human epidemiologic studies showing increased risks of non-Hodgkin's lymphoma and multiple myeloma, some evidence of soft tissue sarcoma, and limited evidence of liver cancer associated with PCP exposure"* citing studies by Demers et al., 2006; Kogevinas et al. 1995 and Hardell et al., 1995, 1994. These four studies (in addition to Collins et al. 2009 and Ruder and Yiin 2011) are briefly reviewed below followed by a weight of evidence evaluation of these data.

Before reviewing the studies which form the basis for the above conclusions, it is necessary to address some key study criteria. Some studies [e.g., International Agency for Research on Cancer (IARC)] have been conducted on large cohorts occupationally exposed predominantly to phenoxy herbicides (2,4-D, 2,4,5-T) with lesser exposure to "chlorophenols." In some of these studies, chlorophenols is not further defined although in most of the herbicide syntheses, it is trichlorophenol and not pentachlorophenol that is used as an intermediate. Consequently, the results of these studies are of less value in assessing possible associations between exposure to PCP and increased risk of cancer. Only when studies demonstrate that exposure to PCP was explicitly considered can results be afforded any weight in a WOE analysis. In addition, in most (if not all) of the herbicide studies, simultaneous exposure to TCDD and other dioxins and furans also occurred. This further undermines and limits the usefulness of these studies in assessing possible associations between exposure to PCP and increased risk of cancer to humans.

Clearly, the most appropriate studies for assessing the carcinogenic potential of PCP are those in which exposure to other possible confounders is limited. In this regard, studies of cohorts exposed either exclusively or primarily to PCP must be afforded more weight than those in which exposure to chlorophenols is used as a surrogate. This issue will be addressed for each study reviewed below.

Hardell et al. (1994)

The case-control study by Hardell et al. (1994) assessed the effects of self-reported exposure to phenoxyacetic acids, chlorophenols or organic solvents on the incidence of histopathologically confirmed NHL. While Hardell et al. state that exposure was "*mostly*" to PCP this is insufficient to conclude that reported results apply specifically to PCP. There were 105 cases of NHL and 335 controls; exposure was assessed by questionnaire that considered lifetime working history (i.e., occupation), various exposures and leisure time activities. Exposure to chlorophenols was

considered low grade if less than one week continuously or less than one month in total and high grade if greater than these parameters. In assessing exposure to low- or high-grade exposure to chlorophenols, there is no indication of the specific chlorophenols to which this designation might apply. However, there is a subgroup designated as having high-grade exposure to PCP although no sub-group with low exposure which eliminates the possibility of establishing a dose-response pattern. High-grade exposure to "chlorophenols" produced an NHL OR of 9.4 (95% CI 3.6-25) and low grade exposure an OR of 3.3 (95% CI 1.6-6.8). High-grade exposure to PCP gave an OR of 8.8 (95% CI 3.4-24). Some of these ORs are not plausible and the wide confidence intervals also cast some doubt on the reliability of the findings (i.e., ***precision of the effects estimates and the robustness of the effects associations***). Hardell et al. (1994) note that most cases and controls had been exposed to 2,4-D and 2,4,5-T so it is not at all clear from the data presented if any of the cases or controls listed as having exposure to chlorophenols also had exposure to these herbicides. Exposure to 2,4,5-T is also likely to involve exposure to TCDD and related compounds that would further confound the results since TCDD is already listed in the RoC as a known human carcinogen. In addition, the tables in this study do not appear to reflect statements in the text that most cases and controls were exposed to phenoxyacetic acids since only 47 cases (out of 105) and 51 (out of 335) controls were listed as having exposure to phenoxyacetic acids or chlorophenols. Consequently, given the above issues, this study should not be relied upon in the RoC process for consideration whether PCP should be listed as a potential human carcinogen. This is particularly the case since a case-control study by the same authors (Hardell and Eriksson 1999) did not show a significantly increased risk of NHL associated with exposure to PCP.

Hardell et al. (1995)

Hardell et al. (1995) conducted a meta-analysis of the data from four studies conducted in Sweden between 1979 and 1990 that investigated possible association between exposure to phenoxy herbicides and chlorophenol and increased risk of STS. There were a total of 434 cases and 948 controls. Similar methods had been used to assess exposure in all four studies which consisted primarily of an extensive self-administered questionnaire assessing working history and specific chemical exposures, smoking habits and leisure time activities. Further information was obtained by telephone interviews if responses were unclear or incomplete. The meta-analysis revealed increased risk for STS associated with exposure to chlorophenols (OR=3.3; 95% CI 1.8-6.1 with no evidence of a dose-response pattern. While exposure to PCP was significantly associated with an increased risk of STS (OR=2.8; 95% CI 1.5-5.4) the data were insufficient to investigate a possible exposure-response trend. It is also important to point out in the context of a potential RoC listing that Hardell et al. (1995) are quite explicit that "*...chlorophenols with their contaminating dioxins and dibenzofurans should be regarded as carcinogenic for STS.*" This acknowledgement alone should eliminate reliance on the Hardell et al. (1995) results as support for listing PCP in the 13th RoC since these results are clearly confounded by exposure to other potential carcinogens.

Kogevinas et al. (1995)

This study was conducted on the IARC international register of workers exposed to phenoxy herbicides, chlorophenols and dioxins. The nested case-control study was limited to investigation of mortality from STS and NHL in over 21,000 workers from 24 cohorts in 11 countries. Exposures to 21 chemicals were estimated based on job records, exposure questionnaires and evaluations of industrial hygiene practices. Eleven cases of STS and 32 cases of NHL occurred within this cohort. For exposure to any chlorophenol (which is clearly not relevant for PCP specifically) the ORs for STS and NHL were 1.29; 95% CI 0.24-6.91 and 1.26;

95% CI 0.52-3.08, respectively. For PCP there were no cases of STS with potential exposure and the OR for NHL was 2.75; 95% CI 0.45-17.0. When exposure to PCP was assessed based on low, medium or high exposure, there were no cases of NHL with low or medium exposure and the OR for high exposure was 4.19; 95% CI 0.59-29.59. To the extent that this study was able to isolate exposure to PCP specifically, there was no significant increase in either STS or NHL associated with exposure. These results suggest that neither exposure to chlorophenols nor to PCP in particular, is associated with increased risk of STS or NHL. The overall conclusion that "*None of the exposures examined in this study was strongly associated with excess risk of non-Hodgkin's lymphoma*" would appear to challenge inclusion in the IRIS (2009) assessment that Kogevinas et al. (1995) was one of the four studies providing "*strong evidence*" for an association between exposure to PCP and NHL. For STS, Kogevinas et al. (1995) did not report a subcohort with PCP exposure alone. Consequently, to the extent that this study was able to isolate a subcohort exposed only to PCP the results are relevant in demonstrating that occupational exposure of almost 14,000 workers does not increase the risk of NHL or STS.

Demers et al. (2006)

This mortality and incidence study assessed the carcinogenicity of PCP and tetrachlorophenol using data from the British Columbia (BC) sawmill workers cohort study which consisted of 27,464 men employed by 14 sawmills for 1 year or more between 1950 and 1995. Estimates of dermal exposure were derived from plant records and interviews with senior employees. External comparisons were made with the general BC population and internal dose-response relationships were assessed using Poisson regression. There were no large or statistically significant excesses of any type of cancers in comparison to the general population, particularly those of *a priori* interest including STS, NHL or MM. Internal analyses, however, showed strong dose-response relationships for non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and kidney cancer. These relationships were strongest when exposure was restricted to PCP rather than to all chlorophenols or tetrachlorophenol. The strength of the dose-response relationship for cancer incidence increased when exposure was lagged by 20 years for NHL and MM and kidney cancer. The authors concluded that dermal exposure to PCP was associated with NHL, MM and kidney cancer, but not with other cancers of *a priori* interest. Noteworthy, is the finding that exposure to PCP was nearly significantly associated with a decreased incidence of STS. In addition, as presented, the study appears to be internally inconsistent. For example, while an exposure-response for NHL is reported with increasing exposure to PCP (Table 4) the rates for both incidence and mortality in Table 2 are at expected levels. This suggests that the low exposure group in Table 4 (less than 1 year of exposure) must have very low incidence and mortality for NHL so the excess in the highest exposed group may be based on a ratio of deficits. However, the size of this study, in conjunction with the ability to identify a cohort specifically exposed to PCP, suggests that these results be afforded weight in a weight of evidence evaluation.

Collins et al. (2009)

This mortality study involved 773 PCP production workers exposed to chlorinated dioxins during PCP manufacturing from 1937 to 1980 with serum dioxin used to estimate exposures to five dioxins (including TCDD). There were eight deaths from NHL in the cohort (SMR=2.4, 95% CI 1.0 to 4.8) with no trend of increasing risk for any cause of death (including NHL) with increasing dioxin exposure. The highest rates of NHL (4 cases) were reported in the highest dioxin-exposed group (SMR= 4.5, 95% CI 1.2 to 11.5) although there was no significant trend for this finding. This cohort had relatively high dioxin exposures as shown by the number of individuals who developed chloracne and with measured serum dioxin levels well above background. As

noted by the authors, "*Other than possibly an increased risk of non-Hodgkin lymphoma, we find no other cause of death related to the mixture of the dioxin contaminants found in PCP.*" This study, although confounded by simultaneous exposure to dioxins (including TCDD) illustrates the weakness of even combined exposure with PCP as a potential cause of HNL.

Ruder and Yiin (2011)

This mortality study involved 2122 PCP production workers from four plants in the Nastional Institute for Occupational Safety and Health exposed to PCP and to dioxin and dibenzofuran contaminants from PCP production. Subcohorts of 720 and 1402 were identified who were exposed to PCP + TCP and PCP (no TCP), respectively. While there was significant mortality from NHL in the total cohort (SMR=1.77, 95% CI 1.03-2.84) mortality from NHL was not significantly increased in the subcohort exposed only to PCP (SMR=1.41, 95% CI 0.64-2.67). Similarly, mortality was not significantly increased in the PCP subcohort for STS (SMR=1.14, 95% CI 0.03-6.36) MM (SMR=1.84, 95% CI 0.68-4.00) or liver cancer (SMR=1.76, 95% CI 0.81-3.35). When analysis was restricted to PCP-exposed white males (N=1776) only mortality from NHL was significantly elevated (SMR=1.98, 95% CI 1.15-3.17); however, this table (i.e., Table 4) appears to be in error as it is labeled as PCP production workers when it actually must be all workers (i.e., TCP +PCP) given that the number is greater than the PCP only exposed workers (N=1402) shown in Table 3. Overall, while this study shows no significant effects of PCP only exposure on mortality from NHL, STS, MM or liver cancer it is unknown why the authors characterize their results as showing "*some support*" for certain cancers (i.e., NHL or leukemia) when the increases were not statistically significant, i.e., "*The findings of this study of an excess of cancers of a priori interest, non-Hodgkins lymphoma and leukemia, provide some support for the carcinogenicity of PCP.*" This is particularly the case since over 90% of the cohort was exposed to additional chemicals during their employment including a number of known or suspected carcinogens. Overall, this study provides no support that occupational exposure to PCP is causally associated with increased risk of NHL, STS, MM or liver cancer.

III. Weight-of-Evidence Evaluation of Key Epidemiology Studies on PCP as Supporting a Conclusion of Causality for NHL, MM, STS or Liver Cancer

Four studies are cited in the IRIS (2009) assessment as support for the conclusion that exposure to PCP is associated with increased risk of NHL, MM, STS and liver cancer with a two additional studies (i.e., Collins et al. 2009 and Ruder and Yiin 2011) published subsequent to the 2009 review. While there are additional studies available these are all compromised by the inability to identify a subcohort exposed only to PCP. Therefore, for purposes of this comment it is assumed that the six studies summarized above are the most appropriate for assessing whether occupational exposure to PCP provides evidence ranging from strong to limited that exposure to PCP causes statistically significant increases in NHL, MM, STS and liver cancer. Consequently, these six studies are considered in this evaluation to determine the extent to which they support the conclusion that there is "***strong evidence*** *from human epidemiologic studies showing increased risks of non-Hodgkin's lymphoma and multiple myeloma,* ***some evidence*** *of soft tissue sarcoma, and* ***limited evidence*** *of liver cancer associated with PCB exposure (Demers et al., 2006; Kogevinas et al. 1995; Hardell et al., 1995, 1994."*

Based on the six studies summarized above, the following causation criteria are systematically applied to the specific effects (i.e., NHL, MM, STS and liver cancer) in order to determine whether the data from these studies support strong to limited evidence of an association with occupational exposure to PCP. Whether these criteria are satisfied by the available data on each of the relevant effects is summarized in Tables 1 and 2 below.

Strength of the Association Clearly, only statistically significant associations between exposure and outcomes are judged to be relevant. Strength of association refers primarily to size of the relative risk which must reach statistical significance. A causal relationship is more credible when the risk estimate (e.g., standardized mortality ratio (SMR) is large and precise (i.e., narrow confidence intervals). The strength of association not only refers to the magnitude of the association, but also embodies the idea that the strength of the association (even if statistically significant) must be believable given the nature of the exposure and the outcomes under investigation. For example, as reported by Hardell et al. (1994) if the OR of 8.8 for STS was indicative of a real association one might expect to see this reflected in other studies which is not the case, e.g., Demers et al. (2006) report close to a significant deficit in STS as a consequence of exposure to PCP. The strength of association attributed to any particular study can be compromised by many factors, including confounding (e.g., exposure to other chemicals), as well as uncertainty in dose measurement or estimation. Consequently, it would be inappropriate to base a potential RoC listing for PCP on any results which are derived from exposure to all chlorophenols rather than PCP specifically.

Consistency of the Association Consistency of association refers to whether a significant association seen in one study is also seen in other studies of similarly exposed populations. This is critical because no single epidemiological study can be considered definitive, particularly the kinds of studies reviewed in this document. This criterion is not satisfied when one study reports an association between exposure to a chemical and a disease and those results cannot be duplicated in subsequent studies. While reliance on only six studies (one of which is a meta-analysis and not a separate study) makes it difficult to assesses the extent to which this criterion is fulfilled, as shown in Table 2 none of the cancer endpoints addressed show a pattern of consistency based on the studies reviewed.

Dose-Response Relationship Any conclusion that exposure to a chemical causes an observed effect is undermined if a correct dose-response relationship does not exist, i.e., if the frequency of the observed effect does not increase with the dose or duration of exposure to a particular chemical. Conversely, the evidence for association is strengthened if increasing exposure is associated with increasing risk. As summarized in Table 2, the only study which reports a significant exposure-response relationship is Demers et al. (2006) which is an insufficient basis for concluding that this criterion is satisfied by the available data.

Temporally Correct Association It should be noted that simply fulfilling the criterion of temporality (i.e., exposure must occur before the onset of disease) is an insufficient basis for concluding that a reported association is causal. Particularly with respect to several studies (e.g., Hardell et al. 1994, 1995), it is unlikely that any exposure to PCP not contaminated with dioxins or furans occurred prior to the onset of disease.

Specificity of Association This criterion was originally intended to judge if one cause was associated with a single effect or disease, i.e., that a finding from one study could be used to predict the outcome of other studies. As noted in EPA (2005) *"Based on our current understanding that many agents cause cancer at multiple sites, and many cancers have multiple causes, this is now considered one of the weaker guidelines for causality."* While the likelihood of a causal interpretation is increased if an exposure produces a specific effect (e.g., one or more tumor types also found in other studies) or if a given effect results from a unique exposure, a causal relationship is undermined if each of several studies on cohorts exposed to

a specific chemical reports a different finding. For example, the finding of increased risk from STS, which has essentially only been reported in the Swedish studies (Hardell et al.), is puzzling. In particular, if exposure to chlorophenhols or PCP and STS were a true cause and effect relationship, other studies with equal or greater exposures should yield similar results (e.g., Demers et al. 2006). The fact that a far more robust study (e.g., Demers et al. 2006) would report almost a significant deficit in STS would appear to invalidate the specificity of the association for this endpoint. In addition, the extensive studies of the large IARC cohort (e.g., Kogevinas et al. 1995) did not reported increased risk of STS associated with exposure to chlorophenols. The striking inconsistency in the reported results from the six studies suggests that this criterion has not been met.

Coherence with Existing Information (Biological Plausibility) Based upon the results of animal studies it can be hypothesized that increased incidence of hepatocellular carcinoma, adrenal medulary neoplasms, and hemangiosarcomas might potentially occur in humans exposed to sufficient amounts of PCP (EPA 2000). However, none of these endpoints has been reported in studies of cohorts exposed to chlorophenols or PCP. In addition, the lack of strong mutagenic potential for PCP suggests that the carcinogenic effects observed in animal studies are likely dose-dependent and secondary to other kinds of toxicity. The finding of increased incidence of hemangiosarcomas (a histologic form of STS) in rats is interesting given the overall WOE in human studies suggesting that exposure to PCP is not associated with increased risk of STS.

Finally, there is also another important consideration pertaining to biological plausibility. Target organ specificity is a key concept which must be addressed in assessing PCP incidence or mortality studies. Studies have shown time and again that human responses to exposures to carcinogens are consistent (i.e. of the same type or nature), although the magnitude of effect might vary among individuals or populations. There are no data suggesting that people with different levels of exposure to the same chemical will get different types of cancers. It is well known that virtually all chemical carcinogens display striking target organ specificity (e.g., cancer chemotherapy, aflatoxin, vinyl chloride, benzene, asbestos, etc.). This is due to the fact that different tissues and organs express different metabolizing, detoxification, and DNA repair processes. Consequently, these organ specific factors respond to carcinogen exposure in different ways. Carcinogen target organ specificity, therefore, renders the striking lack of consistency for tumor types among PCP studies much more likely the result of random findings, confounding due to recognized contaminants or co-exposures to other chemicals rather than causal associations. Simply stated, there is no biologically plausible explanation for how PCP would cause increases in different kinds of cancer in different cohorts or why these chemicals would behave differently than other chemicals that have been causally associated with increases in specific kinds of cancer.

VI. Conclusions

As shown in Table 1, which summarizes the statistically significant findings from the six critical studies, there is at most, limited evidence that NHL or MM might be a consequence of exposure to PCP based on the results of two studies, one of which failed to show a significant exposure-response relationship and was also confounded by simultaneous exposure to dioxins (including TCDD). Unless this finding is corroborated in another study not confounded by another chemical (i.e., TCDD) already listed in the RoC, this level of evidence is insufficient to support a conclusion of causality. The evidence for STS or liver cancer as a consequence of exposure to PCP is even less with the studies suggesting an association with STS confounded by dioxin exposure and no evidence whatsoever of an association with liver cancer. Table 2 illustrates the

extent to which the causation criteria are satisfied by the available data contained in the six studies that would appear to provide the best evidence from which to judge the potential carcinogenicity of PCP.

With respect to the NTP/IRIS (2009) conclusion that there is strong evidence that PCP is causally associated with NHL and MM the WOE clearly does not support such a conclusion and at best only shows limited evidence based on a single study not confounded by exposure to dioxin. The evidence for STS or liver cancer does not even rise to the level of limited as the WOE demonstrates that PCP is not a cause of either of these cancers. However, the key issue that must be addressed concerns a potential RoC listing and whether PCP should be considered as "*known to cause cancer in humans,*" "*reasonably anticipated to cause cancer in humans*" or not be listed at all. "*Known*" can be reasonably eliminated as illustrated by Tables 1 and 2 which show unequivocally that no cancer endpoint can be corroborated (i.e., consistency) based on the key causation criteria of strength of the association (i.e., statistically significant) and a significant exposure response trend. Even "*reasonably anticipated*" is not supported by the data in Tables 1 and 2 for the same reason. Consequently, the only evidence-based conclusion that can be drawn from the data summarized in Tables 1 and 2 is that PCP should not be included for listing in the 13th RoC as either a known or reasonably anticipated human carcinogen.

Table 1. Summary of Statistically Significant Findings from Six Key Studies on Cancer Endpoints Associated with Exposure to PCP

Study	NHL	MM	STS	Liver Cancer	Comment
Ruder and Yiin 2011	No increase in subcohort with PCP-only exposure	No increase in subcohort with PCP-only exposure	No increase in subcohort with PCP-only exposure	No increase in subcohort with PCP-only exposure	2122 U.S. PCP production workers; ability to identify subcohort exposed only to PCP
Collins et al. 2009	Increase in 4 PCP-exposed workers in highest dioxin- exposed (including TCDD) group; no significant D-R trend for mortality	No increase in cohort	No increase in cohort	No increase in cohort	773 workers exposed to chlorinated dioxins (including TCDD) during PCP manufacturing.
Demers et al. 2006	Increase in subcohort with PCP-only exposure; significant D-R trend for incidence, but not mortality	Increase in subcohort with PCP-only exposure; significant D-R trend for incidence & mortality	No increase in subcohort with PCP-only exposure; no D-R trend	No increase in subcohort with PCP-only exposure; no D-R trend	27,464 saw-mill workers; follow-up of Hertzman et al. 1997; 27,464 PCP production workers; ability to identify subcohort exposed only to PCP
Kogevinas et al. 1995	No increase in cohort; no increase based on exposure categories to chlorophenols or PCP	Not mentioned	No increase in cohort; no increase based on exposure categories to chlorophenol or PCP	Not mentioned	21,183 workers exposed to phenoxy herbicides, chlorophenols and dioxins; follow-up Kogevinas et al. 1997; no increase in NHL & STS by years since 1st exposure, duration or job title; no D-R trend
Hardell et al. 1995 (meta-analysis)	Not mentioned	Not mentioned	Increase in cohort based on exposure to chlorophenols and PCP; no D-R trend	Not mentioned	434 STS cases & 948 controls from 4 case-control studies.
Hardell et al. 1994	Significant increase with chlorophenols and PCP; no D-R reported	Not mentioned	Not mentioned	Not mentioned	105 NHL cases & 335 controls; exposure to 2,4-D & 2,4,5-T; TCDD exposure likely; conflicts with Hardell & Eriksson (1999); 442 NHL cases; CP (OR=1.1; 95% CI 0.7-1.8) or PCP (OR=1.2; 95% CI 0.7-1.8); no association with latency or time from last exposure; no apparent trends

Table 2. Extent to Which Causation Criteria Satisfied by Six Key Studies for NHL, MM, STS and Liver Cancer

Study/Cancer Endpoints	Extent to Which the Six Causation Criteria are Satisfied					
	Strength of association	**Consistency of association**	**Temporality**	**Dose-Response**	**Specificity of association**	**Biological plausibility[b]**
Ruder et al. (2011)						
NHL	No	No	Yes	No	No	No
MM	No	No	Yes	No	No	No
STS	No	No	Yes	No	No	Yes
Liver	No	No	Yes	No	No	No
Collins et al. (2009)						
NHL	**Yes[d]**	**Yes?[e]**	Yes	No	Yes	No
MM	No	No	Yes	No	No	No
STS	No	No	Yes	No	No	Yes
Liver	No	No	Yes	No	No	No
Demers et al. (2006)						
NHL	**Yes**	**Yes?**	Yes	**Yes**	Yes	No
MM	**Yes**	**Yes?**	Yes	**Yes**	Yes	No
STS	No	No	Yes	No	Yes	Yes
Liver	No	No	Yes	No	Yes	No
Kogevinas et al. (1994)						
NHL	No	No	Yes	No	No	No
MM	NM[a]	No	Yes	No	No	No
STS	No	No	Yes	No	No	Yes
Liver	NM	No	Yes	No	No	No
Hardell et al. (1994)						
NHL	**Yes[c]**	**Yes?**	Yes	No	Yes	No
MM	NM	No	Yes	No	No	No
STS	NM	No	Yes	No	No	Yes

Liver	NM	No	Yes	No	No	No
Hardell et al. (1995)						
NHL	NM	No	Yes	No	No	No
MM	NM	No	Yes	No	No	No
STS	**Yes**[d]	**Yes?**	Yes	No	No	Yes
Liver	NM	No	Yes	No	No	No

a: **N**ot **M**entioned in study; b: assuming that based on animal studies the only plausible site is hemangiosarcoma; however, if assuming that any positive result in an animal study is indicative of any kind of cancer in humans, this criterion would be satisfied for all endpoints recognizing substantial site concordance between animal and human data for most known human carcinogens; c: not confirmed in case-control study by same authors with 442 NHL cases (Hardell and Eriksson 1999); d: likelihood of confounding due to simultaneous exposure to dioxins (including TCDD); e: given the limited instances where the results of one study have been confirmed in another study (particularly in the absence of confounding by TCDD) it is questionable that this criteria is fulfilled by the available data.