EVALUATION OF PENTACHLOROPHENOL AND PCDD/F EXPOSURE AS RISK FACTORS FOR MULTIPLE MYELOMA

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Introduction:
Pentachlorophenol (PCP) is a heavy duty wood preservative used to treat utility poles. PCP may contain trace levels of certain polychlorinated dibenzo-p-dioxin and polychlorinated dibenzofurans (PCDD/Fs) that are formed during the manufacturing process. Analyses of different PCP products in the late 1980s indicated a mean PCDD/F toxic equivalent (TEQ) concentration of 0.813 ng/mg (U.S. EPA 2008). PCP typically does not contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), but may contain the higher chlorinated dioxins such as 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD.

There are hundreds of former and currently active wood-treating facilities in the U.S., many of which have used PCP. In some areas, concerns have arisen regarding the potential health effects posed to residents living near these facilities. In at least one setting, it has been suggested that residential exposure to PCP (and/or PCDD/Fs present in the PCP) may have posed a risk of multiple myeloma.

Multiple myeloma (MM) is a relatively uncommon malignancy of the plasma cells (Alexander et al. 2007). According to the American Cancer Society, an estimated 20,180 new cases of MM were diagnosed in the U.S. in 2010 (American Cancer Society (ACS) 2011). Known risk factors for MM include increasing age and, race (the risk is highest among African Americans and lowest among Asian Americans). However, to date, there has been no systematic analysis of the literature to assess whether and to what degree PCP and PCDD/Fs might cause or contribute to the risk of MM.

In this review, we evaluate studies involving elevated PCP and/or PCDD/F exposures in occupational and residential settings wherein cancer and/or MM was assessed as a health endpoint. We also consider studies that specifically evaluated wood treatment workers (and nearby residents) at facilities known or suspected to have used PCP. Each study is reviewed to determine: 1) whether the risk of MM is significantly increased in the study population, and 2) when applicable, whether the increase appears to be related to either PCP or PCDD/F exposure.

Methods:
We performed an extensive literature search to gather relevant data for inclusion in our study. Queried databases included but were not limited to PubMed and ToxNet. In addition, we evaluated all Health Consultations and Public Health Assessments published by the Agency for Toxic Substances and Disease Registry (ATSDR; available from http://www.atsdr.cdc.gov/hac/pha/index.asp). We focused on studies involving exposure to 1) phenoxy herbicides and other chemicals where TCDD was a known or suspected contaminant, 2) TCDD itself (industrial accidents), and 3) PCP; we also evaluated studies of wood treatment cohorts.

Results and Discussion:
Table 1summarizes the phenoxy herbicide and TCDD-related studies evaluated in this analysis. The weight of evidence involving TCDD exposures indicates that TCDD is not a risk factor for MM in occupational settings.

PCP-exposed cohorts
Dow Chemical Company was the only company to manufacture PCP in the U.S.; thus, this manufacturing workforce represents the largest PCP-exposed occupational cohort (~ 2,000 workers) in the U.S.. Within the cohort, exposure

Table 1. Summary of Epidemiological Investigations Pertaining to Multiple Myeloma and Phenoxy Herbicide and/or TCDD Exposure

Reference	Year	Population	Study Description	Findings
Fingerhut et al.	1991	Occupational, U.S. Chemical manufacturing (NIOSH study)	Mortality study of 5,172 workers at 12 plants that produced chemicals contaminated with TCDD. Exposure confirmed by measuring serum TCDD levels in 253 members of the cohort.	TCDD exposure. No increased risk.
Asp	1994	Occupational, Finnish pesticide sprayers	Mortality and morbidity study of pesticide (2,4-D and 2,4,5-T) applicators in Finland (n=2,000).	TCDD exposure. No increased risk.
Ott &Zober	1996	Occupational, BASF employees; 1953 accident	Follow up study (through 1992) of 243 individuals exposed to TCDD as the result of a reactor accident. Estimated total TCDD dose for all individuals.	TCDD exposure. No increased risk.
Kogevinas et al.	1997	Occupational, herbicide manufacturing and spraying (IARC Cohort)	Mortality study of workers exposed to phenoxy herbicides or chlorophenols from several countries (n=21,863). Inclusion criteria varied from "ever employed" to "employed at least 1 year." Exposure reconstruction varied: individual job records; questionnaires; measurements of TCDD in serum.	TCDD exposure. No increased risk.
Hooiveld et al.	1998	Occupational, pesticide manufacturing	Mortality study of 1,167 workers employed in pesticide manufacturing (2,4,5-T). Workers exposed to TCDD and other PCDD/Fs by accidental leak. Exposures estimated via questionnaires.	TCDD and PCDD/F exposure. No cases were reported.
Flesch-Janys et al.	1998	Occupational, herbicide manufacturing	Cohort study of 1,583 workers exposed to herbicides contaminated with TCDD.	TCDD exposure. No increased risk.
Steenland et al.	1999	Occupational, U.S. Chemical manufacturing (NIOSH study)	Mortality study of 5,132 workers at 12 plants in that produced chemicals contaminated with TCDD; follow up continued through 1993. Exposure was confirmed by measuring serum TCDD levels in 253 surviving members (from 2 plants) of the study cohort.	TCDD exposure. No increased risk.
Bertazzi et al.	2001	Environmental, Seveso incident 1976	Examined cancer incidence in the Seveso population; follow-up continued from 1977-1996. Reported an increased risk of MM in the medium exposure zone, for females only.	TCDD exposure. No TCDD-related increase in risk.
Bodner et al.	2003	Occupational, Dow Chemical Company workers	Mortality study of 2,187 male chemical production workers with potential TCDD exposure. Evaluated "all cancers," lung cancer, soft tissue sarcoma, NHL and "all remaining cancers."	TCDD exposure. No cases were reported.
t' Mannetje et al.	2005	Occupational, New Zealand phenoxy herbicide manufacturing and spraying	Cohort mortality study of phenoxy herbicides producers and sprayers exposed to TCDD, higher chlorinated dioxins and phenoxy herbicides. The risks for MM and immunoproliferative neoplasms were increased in production workers (SMR=5.51, 95% CI 1.14 -16.1).	Increased risk in production workers (not in sprayers); based on 3 cases.
Pesatori et al.	2009	Environmental, Seveso incident 1976	Examined cancer incidence in the Seveso Population.	Increased risk of MM in certain exposure groups.
McBride et al.	2010	Occupational, New Zealand phenoxy herbicide manufacturers (Dow AgroSciences)	Cohort study examining mortality in New Zealand phenoxy herbicides workers (N=1,134) exposed to TCDD. No cases of MM were reported.	TCDD exposure. No cases of MM were reported.

to chlorinated phenols and their derivatives occurred between 1940 and 1982, and follow-up has been conducted for over six decades. In the first study published on this cohort, Ott et al. (1987) observed two cases of multiple myeloma, which did not represent a statistically significant increase. In a subsequent study by Bond et al. (1989), risk estimates were only reported for cancers of interest, which did not include multiple myeloma. In the remaining analyses, multiple myeloma was either (1) grouped with other lymphopoietic cancers, which were not found to be statistically significantly elevated (Ramlow et al. 1996); or (2) not discussed by the authors (Bodner et al. 2003; Collins et al. 2009). Nonetheless, due to the size of the workforce investigated, and the extensive follow up period, if multiple myeloma was associated with PCP or higher chlorinated dioxins exposure, it is likely that it would have been observed and reported for this cohort.

Two additional investigations have been conducted on PCP-exposed timber workers. Demers et al. (2006) assessed multiple myeloma incidence and mortality among 27,464 Canadian sawmill workers in relation to cumulative dermal exposure to PCP. A statistically significantly increased risk in the highest exposure group was observed (5+ exposure-years), as well as a statistically significant dose-dependent increase in multiple myeloma incidence and mortality. It was noted by the authors that one year of exposure represented 2,000 hours of dermal contact with PCP. Therefore, 5+ exposure-years would be equivalent to 10,000+ hours of dermal contact with PCP. A statistically significantly increased risk for multiple myeloma was not observed in the 1-2 exposure-years or 2-5 exposure-years groups, which correspond to 2,000-4,000 and 4,000-10,000 hours of dermal exposure to PCP, respectively. This study indicates that incidental non-occupational exposure to PCP is not expected to be associated with an increased risk of MM. An additional cohort mortality study was performed by McLean et al. (2007) on 3,891 workers at two New Zealand sawmills. The authors grouped multiple myeloma with other lymphatic and hematopoietic cancers, which were not found to be statistically significantly elevated

Wood-treating cohorts
Wong and Harris (2005) performed a retrospective cohort mortality analysis on a group of 2,179 individuals ever employed between 1979 and 1999 at 11 U.S. wood treating plants. One case of multiple myeloma was observed among salaried employees, which did not represent a statistically significant excess. The authors reported a statistically significantly increased SMR for multiple myeloma in hourly workers (based on 6 observed cases versus 1.5 expected). However, when the SMRs for multiple myeloma were analyzed by length of employment (which was used as a surrogate for cumulative exposure), no relationship was observed. Furthermore, Wong and Harris (2005) also performed a nested case-control study of multiple myeloma; controls were matched based on gender, plant, and similar age (± 5 years). Multivariate analyses based on conditional logistic regression were used to assess the relationship between multiple myeloma mortality and several exposure variables: tobacco consumption, length of employment, and job/exposure categories (including intermittent exposure to preservatives or treated products and intermittent exposure to treated or untreated materials). The authors reported that none of the independent variables were found to be significantly related to multiple myeloma mortality.

Residents living near wood-treating facilities
Dahlgren et al. (2003) analyzed health effects in a population of 1,269 subjects residing in the vicinity of a wood treatment plant in Columbus, MS that historically used PCP. Self-reported cancer prevalence was assessed via questionnaire and compared to a reference population of 479 volunteers residing in Alabama. The authors reported a statistically significantly elevated rate of cancer in the study population versus controls; however, information regarding individual cancer sites was not provided, and multiple myeloma was not mentioned.

In 2000, ATSDR compared the cancer incidence among residents living near the Lincoln Creosote facility to northwest Louisiana's average annual incidence rates; all cases were identified using the Louisiana Tumor Registry (ATSDR 2000). One case of "myeloma" was reported in the study population, but no further discussion or information about this case was provided. In a later study, the ATSDR evaluated cancer incidence data from 1991 to 1999 in individuals residing in the same zip code as the Poles, Inc., wood treatment facility in Idaho (ATSDR 2002). Background rates for the remainder of the state of Idaho were used to calculate the expected number of cases. One (female) case of multiple myeloma was reported. The expected number of cases in females was 0.6, and in the total study population (males and females combined) was 1.3, neither of which represented a statistically significantly increased risk.

In conclusion, the weight of scientific evidence does not indicate an association between residential or occupational exposure to TCDD, PCP, or wood treating operations and multiple myeloma.

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