Chronic Exposure to Chlorophenol Related Compounds in the Pesticide Production Workplace and Lung Cancer: A Meta-Analysis

Rezvan Zendehdel¹, Raana Tayefeh-Rahimian¹*, Ali Kabir²

Abstract

Background: Chlorophenols (CPs) and related phenoxyacetic acids (PAs) are pesticide groups contaminated with highly toxic 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) during production. PAs and CPs exposure is associated with risk of cancer, but the situation regarding lung cancer has not been clearly defined. We proposed a meta-analysis of published researches to evaluate relationship between chronic exposure to PAs and CPs in pesticide production workplaces and the risk of lung cancer. Materials and Methods: After searching PubMed, Scopus, Scholar Google, Web of Sciences until August 2013, the association between chronic PAs and CPs exposure in production workplace and lung cancer was studied in 15 cohort studies. The standardized mortality rate (SMR) and 95% confidence intervals (CI) were collected from the papers. We used random or fixed-effects models, Egger test, funnel plot and meta regression in our analysis. Results: Five papers with six reports were included in the final analysis. The standardized mortality rate for lung cancer from the random model was 1.18 (95% CI: 1.03-1.35, p=0.014) with moderate heterogeneity. Publication bias was not found for included studies in meta-analysis (p=0.9). Conclusions: Our findings has strengthen the evidence of lung cancer from chronic exposure to chlorophenol related compounds (PAs, CPs).

Keywords: Phenoxyacetic acid - chlorophenols - meta-analysis - lung neoplasms
Materials and Methods

Search strategy and study selection

Using key words of different combinations from “chlorophenol”, “phenoxyacetic acid”, “lung cancer” and “dioxin” in PubMed, Scopus, Scholar Google (until 20 pages), and Web of Sciences until August 2013 all publications that investigated the association between chronic CPsR exposures in the pesticide production workplace and lung cancer were identified. In the overlapping studies in the worker populations only the largest study was included in the meta-analysis. By manual search and references checking, we reviewed articles considered to be relevant. To finite interference chemical exposure, publications evaluating cancer mortality in CPsR worker except chronic exposure in production factory were emitted in this study. The initial search yielded 508 papers. After reviewing titles and abstracts, 15 eligible papers were selected. By evaluating the full text of these papers ten articles were excluded due to their partial or complete overlap. While more than 30% follow up during of a study (Manuwald et al., 2012) was independent from a multicenter report (Kogevinas et al., 1997), once it was included in the meta-analysis and again excluded from our study. Since one of the studies (Collins et al., 2009) has two individual cohort investigations with different entry criteria such as type of CPs exposure, we included this cohort of the study as two independent investigates (Figure 1).

Quality assessment

The quality of studies was assessed by two matched reviewers (RZ and RTR) independently based on the STROBE guideline [www.strobe-statement.org available at 8 April 2013]. Any disagreement was addressed by a joint reevaluation of that paper. If disagreement remained, the third person (AK) also participated in quality assessment of that paper in joint session. Finally, mean score was reported, if discrepancy did not resolve.

Data extraction

Two independent matched reviewer (RZ and RTR) who were blind about the name of the journals and authors, extracted data from papers. There were information in the papers such as type of study (cross sectional, case-control, or cohort), country and year of the study, sample population (general pop, hospitalize cases, cancer registry, or other), sample size, male percent, response rate, subgroup prevalence (lower and upper 95%CI in all cases and separately in men and women), comorbidities, Toxic Equivalent (TEQ) assessment for dioxin exposure, standardized mortality rate (SMR), number of population under study (target population), follow up years, exposed time (years), number of authors, journal impact factor (IF), place of exposure. Some information were not in the papers and we E-mailed to corresponding authors to answer some of our questions (plasma dioxin level, latency of exposure, and some other SMRs); but they did not answers some of the questions (district, area (rural/urban), sampling method).

Any conflict in data abstraction was resolved by consensus, referring back to the original article. The third author (AK) participated for consensus, if that would be needed.

Statistical analyses and ethics

The meta-analysis was designed according to STATA 11. We evaluated the heterogeneity of the studies with Q test. When the p value of the Q test was ≥0.1, we conducted fixed-effects model of Mentel-Henzel test, otherwise random-effects modeling based on DerSimonian Laird method was used. Quantification of heterogeneity was based on I². Publication bias was evaluated based on Egger test and funnel plot. SMR of lung cancer was plotted versus standard error for each study. If plot symmetrically scattered around funnel, there is no bias for publications. Meta-regression was used to assess the significant sources of heterogeneity while we consider all probable variables which could change τ².

Results

The meta-analysis was carried out for five cohort studies (Kogevinas et al., 1997; Burns et al., 2001; Collins et al., 2009b; Ruder et al., 2011; Manuwald et al., 2012) with six reports where investigate causes of lung cancer among workers of CPsR plants. Collins et al. study (Collins et al., 2009) from the USA evaluated...
two individual investigations with different types of CPs exposure. Among the studies, one multicenter analysis from IARC publications included 36 studies from previous reports (Kogevinas et al., 1997). Overall, a total of 27865 workers in CPsR production involved in the meta-analysis (Table 1). The funnel plot is represented in Figure 2 where publication bias was not found for included studies as the same as Egger’s test showed (p=0.9).

The results of random effect analysis for six reports increased 18% of the lung cancer risk (SMR: 1.03-1.35, p=0.014) significantly (Figure 3). However, there is medium heterogeneity (Q statistics p=0.093; I²=46%) for six reports. We have removed the study of Manuwald et al. (2012) from analysis because of partial overlapping with Kogevinas et al. (1997). By excluding this study in the absence of heterogeneity (Q statistics p=0.2; I²=31.5%) lung cancer risk 13% increased (SMR=1.13, 95% CI: 1.04-1.23; p<0.004).

The results of subgroup based on the specific study characteristics have been presented in Table 2. According to fixed-effects model, SMR of lung cancer for TCDD-exposed population was 1.12 (95%CI: 1.01-1.27) and significantly increased (Kogevinas et al., 1997; t Mannetje et al., 2005; McBride et al., 2009; Jiang et al., 2012). When focused on the latency of CPsR exposure (Fingerhut et al., 1991; Becher et al., 1996; Ramlow et al., 1996; McBride et al., 2009) and lung cancer diagnosis, SMR for over 20 years latency was 1.38 (95%CI; 1.06-1.78; p=0.01) where as other groups represent any increased risk for lung cancer.

When stratified two studies according to different TCDD levels (Collins et al., 2009; Manuwald et al., 2012), the SMR for lung cancer decreased by increasing TCDD levels (according to random effects model) but not significantly. Our results provide the need of more supports for detailed quantitative conclusion in TCDD levels.

### Table 1. Details of Included Studies in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Type of study design</th>
<th>Period of observation</th>
<th>Publication year</th>
<th>Total exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>James J Collins (22)</td>
<td>USA</td>
<td>cohort</td>
<td>1937-1980</td>
<td>2009</td>
<td>774</td>
</tr>
<tr>
<td>Manolis Kogevinas (23)</td>
<td>European (multicentre)</td>
<td>cohort</td>
<td>1939-1992</td>
<td>1997</td>
<td>21863</td>
</tr>
<tr>
<td>Avima M Ruder (18)</td>
<td>USA</td>
<td>cohort</td>
<td>1940-2005</td>
<td>2011</td>
<td>2122</td>
</tr>
<tr>
<td>Ulf Manuwald (19)</td>
<td>Germany</td>
<td>cohort</td>
<td>1952-2007</td>
<td>2012</td>
<td>1589</td>
</tr>
<tr>
<td>C J Burns (21)</td>
<td>USA</td>
<td>cohort</td>
<td>1945-1994</td>
<td>2001</td>
<td>1517</td>
</tr>
</tbody>
</table>

### Table 2. Subgroups Investigated for the Risk of Lung Cancer

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of study models</th>
<th>SMR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCDD exposed</td>
<td>Fixed</td>
<td>1.12 (0.98-1.27)</td>
<td>0.09</td>
</tr>
<tr>
<td>No TCDD exposed</td>
<td>effect</td>
<td>1.03 (0.87-1.21)</td>
<td>0.73</td>
</tr>
<tr>
<td>Latency period (year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>Fixed</td>
<td>0.91 (0.54-1.53)</td>
<td>0.7</td>
</tr>
<tr>
<td>15</td>
<td>effect</td>
<td>0.96 (0.63-1.45)</td>
<td>0.84</td>
</tr>
<tr>
<td>&gt;20</td>
<td></td>
<td>1.37 (1.065-1.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma TCDD level (ppt-years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-0.14</td>
<td>Random</td>
<td>1.45 (0.81-2.58)</td>
<td>0.21</td>
</tr>
<tr>
<td>0.15-0.824</td>
<td>effect</td>
<td>1.33 (0.88-2.01)</td>
<td>0.177</td>
</tr>
<tr>
<td>&gt;0.825</td>
<td></td>
<td>1.15 (0.66-1.74)</td>
<td>0.62</td>
</tr>
<tr>
<td>Component exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorophenol</td>
<td>Random</td>
<td>0.89 (0.66-1.19)</td>
<td>0.422</td>
</tr>
<tr>
<td>Phenoxy acids</td>
<td>effect</td>
<td>1.20 (0.97-1.49)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mixture</td>
<td></td>
<td>1.18 (0.87-1.61)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

In six reports reviewing chronic CPsR exposure was...
evaluated for three groups while dioxin contamination is the main cause of toxicity. However, three studies related to CPsR, two papers reported PAs exposure and others published exposure setting of the PAs and CPs mixture. With respecting exposure setting (Chlorophenol vs phenoxy acids vs mixture), the SMR for lung cancer was 1.2 (95%CI; 0.97-1.49; p=0.09) in PAs exposures whereas for others increased not significantly.

After including all mentioned assessed variables in data extraction like origin country of study, year of study, sample size, type of cohort (retrospective/prospective), quality score, male percent, response rate, subgroup prevalence (lower and upper 95%CI in all cases and separately in men and women), comorbidities, Toxic Equivalent (TEQ) assessment for dioxine exposure, number of population under study (target population), follow up years, exposed time (years), number of authors, journal impact factor (IF) and place of exposure, only origin country of study had the nearer borderline but not significant (p=0.183). So, we did not find any source of heterogeneity.

Discussion

Associations between the chemicals and lung cancer in occupational exposure have been reviewed in several publications (Beaver et al., 2009; Leem et al., 2010; Van Tongeren et al., 2012; Rim, 2013). Last evaluation focused on lung cancer in TCDD exposure (Boffetta et al., 2011). CPsR pesticide has significant contaminated levels of dioxins. We traced 27865 workers with job histories of CPsR exposure. The results of our meta-analysis indicate significant association between chronic CPsR exposure and increased risk of lung cancer. By Meta-analysis of six published reports which each of study has limitations, our analysis present moderate between-study heterogeneity. Finally heterogeneity was not appeared by excluding the partial overlapped study of Manuwald et al (2012).

Four reports revealed the relation of exposure latency and lung cancer risk. Fingherhut MA and Becher H (Fingerhut et al., 1991; Becher et al., 1996) reported a non-significant increase of lung cancer in workers exposed to CPsR after 20 years latency of exposure. Our analysis supports a significant of 38% increased in SMR for population with over 20 year’s latency of exposure. However, two additional studies provide further information where the quantitative association between plasma TCDD level and lung cancer was reported. The results of this study, suggest a positive association between different TCDD concentration exposure and lung cancer but not statistically significant. It seems, they provide further support for quantitative judgment. Moreover, the risk of lung cancer amplified in the TCDD exposed group significantly.

By regarding the relationship between the exposure setting and lung cancer, this should be highlighted that PAs exposures serve as significant foundation in lung cancer risk. However, one limitation of this study is bias estimation in different publications. Although some studies applied adjusted estimates to minimize bias estimation but some others did not provided. For example, McBrine D et al (McBrine et al., 2009) focused on TCDD as CPsR contaminated exposure risk factors for cancer, but TCDD background exposure has not described truly in this topic.

In vivo researches on TCDD component have confirmed its carcinogenetic effect on lung (Walker et al., 2007). These chemicals produce biochemical changes producing tumor cells in lung (Walker et al., 2005). Since, aryl hydrocarbon receptor activation mediates the tumorgenicity of dioxin compounds, MicroRNAs expression by TCDD regulate lung cancer promotion of these compounds (Singh et al., 2012). Overall, IARC multinational study and NIOSH Dioxin Registry report a wide range of lung cancer in workplace site (Boffetta et al., 2011). Our findings are comparable with the result of past studies. Ultimately, the results of our meta-analysis strengthen the evidence of occupational exposure to CPsR contaminated with TCDD and increased risk of death from lung cancer.

According to our meta-regression, we did not find any significant association between each one of factors like origin country of study, year of study, sample size, type of cohort, quality score and SMR of lung cancer. It can be due to small number of studies was included in our meta-analysis. In conclusion, our findings has strengthened the evidence of occupational chronic exposure to Chlorophenol related compound (PAs, CPs) and increased risk of death from lung cancer.

Acknowledgements

We appreciate all published papers in this field which provide us to explore more detailed association between Chlorophenol related compounds and lung cancer by doing meta-analysis.

References


Burns CJ, Beard KK, Cartmill JB (2001). Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update. Occup Environ Med, 58,
24-30.
Singh NP, Singh UP, Guan H, Nagarkatti P, Nagarkatti M (2012). Prenatal exposure to TCDD triggers significant modulation of microRNA expression profile in the thymus that affects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Newly diagnosed without treatment</th>
<th>Newly diagnosed with treatment</th>
<th>Remission</th>
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<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Concurrent chemoradiation</th>
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<tr>
<td>0</td>
<td>38.0</td>
<td>38.0</td>
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<td>51.1</td>
<td>25.0</td>
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<td>25.0</td>
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<td>27.6</td>
<td>51.7</td>
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<td>50.0</td>
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<td>75.0</td>
<td>38.0</td>
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<td>33.1</td>
<td>30.0</td>
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