Evidence-Based Practice Group Answers to Clinical Questions

"Electrician Work in Petroleum Refineries and the Development of Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)"

A Rapid Systematic Review

By

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Clinical Services – Worker and Employer Services

About this report

Electrician Work in Petroleum Refineries and the Development of Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

To determine whether there is any evidence to support a causal association between working as an (industrial) electrician in petroleum refineries and the development of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

Methods

In order to investigate the possibility of a causal association between working at petroleum refineries as an industrial electrician and subsequent development of leukemia (specifically AML type), a comprehensive literature search was conducted on August 9, 2018.

The literature searches were done on commercial medical literature databases as well as occupational health related databases. These database include:

- BIOSIS Previews® (1969 to 2008), Embase® (1974 to 2018 August 08), Medline Epub Ahead of Print®, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline® (1946 to August 08, 2018). These databases are available on the Ovid® platform.
- MSDS (Material Safety Data Sheets from manufacturers and suppliers); CHEMINFO® (comprehensive health and safety information on pure chemicals); FTSS® (Fiche techniques sur la securite des substances); RTECS® (Registry of Toxic Effects of Chemical Substances); OSH References including OSHLINE®, NIOSHTIC®, NIOSHTIC-2®, HSELINE®, CISILO®, Canadiana®; Canadian enviroOSH Legislation (legislation for British Columbia, Alberta, Saskatchewan, Manitoba, Yukon, Northwest Territories, Nunavut and Canada (Federal)); OSH Answers® (Answers to hundreds of frequently asked health and safety questions); INCHEM (Chemical publications from United Nations agencies); Workplace Health Promotion Resources® (workplace health information); CHEMINDEX® (Chemical names, CAS Registry Numbers and Synonyms); WHMIS Classifications (WHMIS hazards of common workplace chemicals); Fatality Reports® (Information on workplace fatalities including preventive measures). These databases are available through the Canadian Centre for Occupational Health and Safety® (CCOHS) Web Information Service.

Combinations of keywords were employed in these searches. Searches on Ovid® platform employed the following combinations of keywords:

1. (((petroleum **OR** oil **OR** gas) **AND** refiner$)) **AND** (industrial **ADJ** electrician$)
   No published study was identified through this search.
2. (((petroleum **OR** oil **OR** gas) **AND** refiner$)) **AND** electrician$ **AND** (acute **ADJ** myeloid **ADJ** leukemia)
   No published study was identified through this search.
3. (((petroleum **OR** oil **OR** gas) **AND** refiner$)) **AND** electrician$ **AND** (myelodysplastic **ADJ** syndrome$)
   No published study was identified through this search.
4. (((industrial **ADJ** electrician$) **OR** electrician$) **AND** ((petroleum **OR** oil **OR** gas) **AND** refiner$) **AND** leukemia)
   No published study was identified through this search.
5. (acute **ADJ** myeloid **ADJ** leukemia) **AND** ((petroleum **OR** oil **OR** gas) **AND** refiner$)
   Nine[1,12,18,22,23,27,33,36,40] published studies were identified through this search.
6. (myelodysplastic **ADJ** syndrome$) **AND** ((petroleum **OR** oil **OR** gas) **AND** refiner$)
   Eight[2,20,28,30,31,34,35,38] published studies were identified through this search.
7. (acute **ADJ** myeloid **ADJ** leukemia) **AND** electrician$
   Three[13,21,25] published studies were identified through this search.
8. (myelodysplastic **ADJ** syndrome$) **AND** electrician$
   One[5] published study was identified through this search.
9. ((industrial **ADJ** electrician$) **OR** electrician$) **AND** benzene
   Four[5,24,29,39] published studies were identified through this search.
10. (((industrial **ADJ** electrician$) **OR** electrician$) **AND** leukemia)
    Nineteen[3-10,12,13,15-17,19,21,25,26,32,37] published studies were identified through this search.

Searches on CCOHS Web Information Service site employed the following keywords:

11. (acute myeloid leukemia) **AND** electrician
12. (myelodysplastic syndrome$) **AND** electrician

None of the searches on CCOHS yielded any relevant study.

Overall, forty [1-40] published studies were identified through these searches. Upon examination of the titles and abstracts of these 40[1-40] studies, seventeen[1,3,5,6,12,18,19,22,23,26,27,30,33,35,36,38,40] studies were thought to be relevant and were retrieved in full for further appraisals.
No limitations, such as on the date or language of publication, were implemented in these literature searches.

Manual searches were also conducted on the references of the articles that were retrieved in full. No relevant studies were further identified through these manual searches.

In order to conclude that a causal association exists between an exposure (c.q. being employed at pulp and paper mill) and disease (c.q. AML or leukemia in general) in epidemiological studies, certain criteria need to be fulfilled[46]. These criteria include strength of the association, consistency (i.e. a relationship is observed repeatedly), specificity (i.e. an exposure influences specifically a particular outcome or population), temporality (i.e. the exposure must precede the outcome it is assumed to affect), biological gradient or dose-response relationship (i.e. the outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory), biological plausibility (i.e. the observed association can be plausibly explained), coherence (i.e. an observed causal conclusion should not fundamentally contradict present substantive knowledge), experiment (i.e. causation is more likely if evidence is based on randomised experiments) and analogy (i.e. analogous exposures and outcomes an effect has already been shown) [47].

Results

Leukemia and acute myeloid leukemia[41-45].

Leukemia arises from malignant transformation of hematopoietic stem or progenitor cells that originate in the bone marrow, lymph nodes, and/or other lymphoid tissue with immune function. A small pool of stem cells (which persists throughout an individual's lifetime) differentiates to early precursors, then divides into multiple subtypes, and ultimately produces large numbers of end-stage cells of myeloid and lymphoid lineage progeny. To date, the four major categories of leukemia include acute myeloid (including acute monocytic), chronic myeloid, acute lymphocytic, and chronic lymphocytic leukemia. The rarity of individual leukemia subtypes and limitations of earlier classifications of leukemia hindered the investigation for risk factors of leukemia, despite rapid advances made toward our knowledge of the molecular and immunologic underpinnings of leukemo-genesis.
Acute leukemia, of either the myeloid or lymphoid types, are infrequent diseases, but they are highly malignant neoplasms responsible for a large number of cancer associated deaths. Within these acute leukemia types, acute myeloid leukemia (AML) is the most common type of leukemia in adults (about 25% of all leukemias) and have the lowest survival rates. Worldwide, the incidence of AML is highest in the USA, Australia and Western Europe.
Although AML can occur in any age group, AML is most commonly diagnosed in older adults, with a median age at diagnosis of 68 years. Similarly, myelodysplastic syndromes (MDS) are also more typically diagnosed in older people, with a median age at diagnosis of 65–70 years; less than 10% of the patients are younger than 50 years. The age-adjusted incidence rate of AML in the USA is approximately 3.7 per 100,000 persons with evidence suggesting that the incidence is higher in the older age groups, while the annual incidence of MDS is about four cases per 100 000 people (reaching 40–50 per 100 000 after age 70 years). In the USA, the age-adjusted mortality rate for AML is 2.7 per 100,000. This mortality rate is also influenced by age and sex; the highest rates are observed in patients > 80 years of age, as well as observed rates being higher among males.

Several risk factors have been associated with AML, including:

- Advanced age
- Environmental exposures such as cigarette smoking, benzene, organic solvents and pesticides

- Cytotoxic chemotherapy including alkylating agents (e.g. cyclophosphamide), topoisomerase II inhibitors (e.g. epipidophyllotoxins, anthracyclines), taxanes and platinum agents
- Ionizing radiation
- Antecedent hematologic disorders, such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms, aplastic anemia or paroxysmal nocturnal hemoglobinuria
- Clonal hematopoiesis of indeterminate potential
- Familial germ line predisposition for acute leukemia or myelodysplastic syndromes, including CEBPA, DDX4, RUNX1, ANKRD26, ETV6, GATA2 or SRP72 germ line mutations or 14q32.2 genomic duplication (ATG2B/GSKIP)
- Cancer predisposition syndromes, including Li Fraumeni syndrome (TP53) or germ line BRCA1/BRCA2 mutations
- Bone marrow failure syndromes, including dyskeratosis congenita, Fanconi anemia and Shwachman-Diamond syndrome
- Other genetic syndromes, including Down syndrome, Klinefelter syndrome, Patau syndrome, Kostmann syndrome, Bloom syndrome, Wiskott-Alrich syndrome or Neurofibromatosis type I.

For the development of MDS, identified risk factors include:

- Antineoplastic agents, including alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, lomustine or melphalan; Topoisomerase II inhibitors such as daunorubicin, doxorubicin, etoposide, mitoxantrone or razoxane; purine analogues such as fludarabine and others
- Radiotherapy or environmental factors including tobacco, ionising radiation, benzene exposure (and industrial hydrocarbons) as well as agricultural compounds such as pesticides, herbicides and fertilisers.

It should be noted that the cause of MDS is known in only 15% of cases.

Critical appraisal of the literature:

Of the seventeen[1,3,5,6,12,18,19,22,23,26,27,30,33,35,36,38,40] studies that were retrieved in full, two studies[18,30] were not relevant to the objective of this systematic review; two studies[33,40], although investigating mortality within a petroleum refinery setting, did not investigate the role of occupation within the refinery in association with the development of AML or MDS; one[26] study investigated the mortality patterns of the U.S. members of the International Brotherhood of Electrical Workers but limited their study to

residential or construction sites electrician; a further ten studies[1,5,6,12,22,23,27,35,36,38] did not provide any data specific to electricians/electrical work in their reporting of morbidity or mortality among refinery workers. As such, these fourteen[1,5,6,12,18,22,23,27,30,33,35,36,38,40] studies will not be discussed further.

By employing five of the eight available Swiss regional cancer registries, which together covers approximately 40% of the Swiss population and recorded the occupation for cancer patients, Bouchardy et al.[3] reported on the cancer risk by occupation (and socio-economic status) among men (Level of evidence 3. Appendix 1). With regard to electricians, the authors observed a 2.5-fold increased risk of pleural mesothelioma and a 1.2-fold increased risk of lung cancer (95% CI 1.1–1.4), confirming potential asbestos exposure among electricians. The authors also hypothesized on the potential, and still controversial, association between leukemia and exposure to electromagnetic fields, noting an approximate twofold increased risk for acute leukemia (OR 1.9). The authors did not provide any data specifically regarding working at refineries and the potential association with acute leukemia. *It should be noted that although this study included 58,134 incidents (cases) of cancer (from the period of 1980-1993), this data came from administrative databases where the data may be skewed by potential biases (such as misclassification of the occupation and exposure; selection bias may have occurred, perhaps due to the lack of consideration for the migration of workers) and confounders (such as whether the worker was a smoker/non-smoker/never smoker) – such information may not be available and hence is not taken into account in its analysis. Further, in this particular study, multiple comparisons were demonstrated without adjustment to the level of type 1 error.*

By employing the New Zealand Cancer Registry database, Pearce et al.[19] conducted a case-control study (Level of evidence 3. Appendix 1) investigating the potential increase in the risk of developing leukemia among electrical workers. The study included all male patients registered with the New Zealand Cancer Registry for the period of 1980-1984 who were aged ≥ 20 years at time of registration. It should be noted that the New Zealand cancer registrations include a brief description of each individual's current or most recent occupation at the time of registration. Of the 24,762 eligible participants, occupational information was available for 19,904 (80%). The analysis focused on various types of 'electrical work' which had been previously reported to have increased leukaemia risks. These types of 'electrical work' included: electrical and electronic engineers, electrical and electronic technicians, electrical fitters, electronic equipment assemblers radio and television repairers, electricians, telephone installers, linemen and power station operators. Unfortunately, no information on potential exposure

was available. The authors reported that there was an elevated leukaemia risk in New Zealand electrical workers (odds ratio (OR) = 1.6, 95% confidence interval (CI) 1.04-2.5), but little evidence of increased risks for other cancer sites. Pearce et al. also found that, contrary to other published studies, the increased risk was primarily for chronic leukaemia (OR = 2.1) rather than acute leukaemia (OR = 1.3), and for lymphatic leukaemia (OR = 1.7) rather than myeloid leukaemia (OR = 1.2). Further, the authors found that the increased risk was strongest for certain categories of electrical work including radio and television repairers (OR = 7.9, 95% CI 2.2-28.1), electricians (OR = 1.7, 95% CI = 0.7-3.8), linemen (OR = 2.4, 95% CI 1.0-5.7) and power station operators (OR = 3.9, 95% CI 1.0-15.2). *It should be strongly noted that the data for this study came from administrative databases where data may be subject to potential biases (such as misclassification of the occupation or selection bias occurring due to not accounting for the migration of workers) and confounders (such as on the smoking/non-smoking status of the worker); this type of information may not be available and hence is not taken into account in its analysis.*

Summary

- At present, there is no data to support a potential (causal) association between working as an (industrial) electrician in refineries and the development of AML or MDS.
- At present, there is conflicting evidence as of the types of leukemia (acute vs. chronic; myeloid vs. lymphatic) that may increase its risk, if any, among electricians in general.

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence

(adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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