Effects of Bauxite and Alumina Exposure on Mortality due to Cancer - Meta-analysis

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ABSTRACT

Bauxite is an ore from which Aluminium is produced. Malaysia, once the leading producer of bauxite has reduced production as mining activity has caused community outrage. Due to concerns about health concerns, rising pollution and environmental hazards, the government has revoked the licenses of bauxite miners. We therefore did a meta-analysis to assess the relationship between exposure to Bauxite and Alumina with mortality of overall cancer as well as specific types of cancers. Participants of were individuals of all ages who were exposed to Bauxite and Alumina while working in Bauxite mines and Alumina refineries.

Exposure to bauxite and alumina did not cause variations in mortality of overall cancer and specific types of cancer such as cancer of lip, cancer of the oral cavity and pharynx, cancer of digestive organs and others. We conclude that there is no evidence that bauxite or alumina exposure cause increase mortality due to cancer but due to the small number of studies included in this review, we recommend more cohort studies to be done in future.

KEY WORDS

Bauxite alumina exposure, Cancer mortality, Review

INTRODUCTION

Malaysia was once the world's top procedure of Bauxite which could bring revenue for the country and increase employment. However, there has been community outrage on the hazards of bauxite mining and aluminium processing. There are postulations that even though chronic diseases are not apparent, they may appear later due to the slow pathogenesis.

Bauxite and alumina mining throughout the world have resulted in community outrage due to their concerns on environmental and health issues. Bauxite, an ore, is the world's main source of Aluminium. French chemist Henri Sainte-Claire Deville named the mineral "bauxite".[1] Donoghue et al. found that the most important risks of bauxite mining and aluminium processing were related to noise, ergonomics, trauma, and caustic soda splashes of the skin/eyes.[2] Other risks of note were related to fatigue, heat, solar ultraviolet and for some operations tropical diseases. Donoghue at al noted that exposure to Bauxite dust was not related to decrements in lung function and association with cancer.[2]

Description of the exposure

Bauxite is a group of aluminium oxides, with the term denoting the economically most important mixture of these minerals.[3] The importance of Bauxite is that it is regarded as the primary ore of the metal aluminium. Bauxite is further classified according to its commercial application, such as refractory, abrasive, cement, chemical and metallurgical. Of all bauxite mined, approximately 85% is converted to alumina (Al_2O_3) for the production of aluminum metal, a further 10% is utilized for nonmetal uses as various forms of specialty alumina, and the remaining 5% is used for non-metallurgical bauxite applications.[4]

How the exposure might relate to mortality

Both bauxite and alumina dusts are considered as insoluble low-toxicity dusts. Though there have been no consistent associations with respiratory symptoms or lung functions with either dusts, high exposure to alumina has been associated with scanty, small irregular opacities in the lungs.[5-7] Benke et al. further noted workers in bauxite

and alumina refineries to be possibly associated with radiographic abnormalities on lungs.[8] In addition, workers exposed to dusty jobs, irrespective of dust type, are at risk to heart disease risk factors through inflammatory changes in blood vessels.[9-10] Quartz is approximately 3% of respirable bauxite dust, which is approximately 30% of inhalable bauxite, so some silica exposure occurs which in the form of respirable, crystalline silica has been noted as risk factor for non-malignant respiratory disease and lung carcinogen.[11-14]

Why it is important to do this review

In the year 2000, 22 countries reported bauxite mine production with Australia, Brazil, Guinea, and Jamaica accounting for about 70% of the total bauxite mined in 2000.[15] In Malaysia, annual output of bauxite ore increased from a little over 200,000 tons in 2013, to nearly 20 million tons in 2016 making the nation one of the world's top producers of bauxite in 2016.[16] However as a result of concerns on health concerns and other issues such as rising pollution, and environmental hazards, Malaysia has banned mining activities on bauxite and alumina.[16]

Internal comparisons among individuals and especially workers exposed to bauxite and alumina have shown some evidence of associations with malignancy (especially pleural mesothelioma), circulatory, cardiovascular and cerebrovascular disease which was not seen in external comparisons.[17]

Although bauxite and alumina mining have been around for many decades, there is lack of literature with regards to the hazards of bauxite mining. Abdullah et al. postulate that even though chronic physical illnesses are not apparent now due to its slow pathogenesis, diseases may appear later on if not properly addressed and controlled.[18]

To our knowledge, there has been no review anywhere in the literature on the effects of exposure towards bauxite and alumina on the mortality as a result of malignancy among individuals such as workers in the mining industry and population residing nearby these industries.

The objective of this study was to assess the relationship between exposure to bauxite and alumina with mortality due to various types of cancers. The criteria for including studies for this review were cohort studies involving individuals of all ages who are exposed to bauxite and alumina. Outcomes studied were incidence due to overall cancer and other specific types of cancer.

We obtained relevant studies from Pubmed, Google Scholar, Science Direct and Cochrane Library using the words Bauxite, Alumina, Aluminium Oxide, cancer, specific types of cancer. The last search was done on 10th October 2017. We obtained full texts through the Ministry of Health Virtual Library and the Library of Melaka Manipal Medical College Malaysia.

Data collection and analysis

The two review authors (TT and ALA) assessed the eligibility of the studies independently and subsequently scrutinized and verified the studies to be entered. We settled and solved disagreements through discussion. Full texts of all the articles were obtained. The review authors perused and independently selected the studies. We settled disputes by going through the studies together with further discussion. We assessed exposed and unexposed from same population (selection bias), assessment of exposure (assessment exposure bias), absence of outcome at start (outcome bias), presence of prognostic variables / confounders (presence confounder bias), adjustment for prognostic variables / confounders (adjust confounder bias), assessment of outcome (assess outcome bias), adequacy of follow-up (follow-up bias), similar co-intervention between groups (co-intervention bias). The risks of bias were assessed as low risk, unclear risk and high risk.

We carried out meta-analysis via the use of Review Manager software (RevMan 2014) for the trials that were eligible. We utilized fixed-effect meta-analysis model for trials that were sufficiently similar with no significant heterogeneity. We made use of risk ratio or mean differences as summary measures where applicable. We used the Chi^2 test for heterogeneity with significance level $P < 0.1$ and assessed the degree of heterogeneity by means of the I^2 statistic. I^2 value of 30% or more was regarded as having moderate heterogeneity.

We made extensive searches in an attempt to reduce and minimise publication and reporting biases. Selective outcome reporting was assessed within studies as part of risk of bias assessment. We had initially aimed to utilise funnel plot analysis to assess for publication bias; however, as there were insufficient studies with similar outcome measures, we did not perform the funnel plot analysis.

We had planned to carry out a sensitivity analysis to explore the effects of the risk of bias of the studies and thereafter by excluding trials with a high risk of bias for this domain. However, we did not proceed to perform the analysis as there were insufficient trials with similar outcome measure in this review.

RESULTS

We obtained and searched seven records related to the topic, of which all records were identified through database searching MEDLINE, PubMed, Google Scholar and the Cochrane Library (Fig. 1). There was no other record identified from other sources.

We further acquired the full-text publication for all seven studies. We proceeded to remove six records from this list that did not fully fulfill the inclusion criteria, leaving us a total of one study.

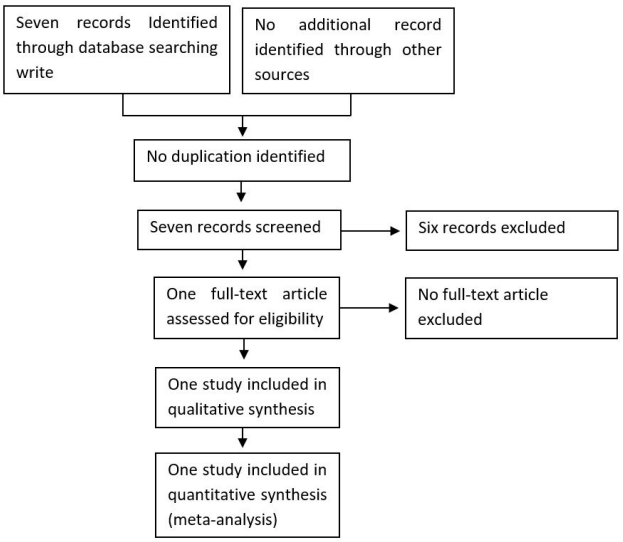

Figure 1. Flow chart-selection of studies for inclusion

We included one cohort study that met our inclusion criteria. This study consisted of 6485 employees who further comprised of 5828 men and 657 women (Table 1). Fritschi et al. followed up former and current employees of a large aluminium company as long as they had been employed for at least 90 days at any of the bauxite mines or alumina refineries on or after January 1983.[17]

Table 1. Characteristics of included study – Fritschi 2008[17]

Methods	Cohort Study
Participants	6485 employees comprising 5828 males and 657 females, mean age 29.0 years.
Exposure	Bauxite and alumina
Outcomes	Mortality and incidence of various types of cancer such as cancer of the colorectal, prostate, bladder, kidney, lung, mesothelioma and overall cancer. In addition mortality and incidence of circulatory diseases, respiratory diseases, injuries / trauma.

We analysed outcomes which included mortality due to overall cancer, and other specific types of cancer such as cancer of lip, cancer of the oral cavity and pharynx, cancer of digestive organs, cancer of respiratory and intrathoracic cancer, melanoma, mesothelioma, cancer of male genital organs, urinary tract cancer, cancer of brain and central nervous system, cancer of thyroid, endocrine cancer, leukaemia and lymphomas.

In Fritschi et al. participants comprised of employees taken from the Bauxite mines or Alumina refineries.[17] We assessed selection bias as low risk as these employees had the same point of origin with regards to the population group.

Fritschi et al. did not provide details of how exposure information was obtained.[17] Though the study mentioned that employees without job history information were excluded from the analysis, the study mentioned that work histories of employees between 1996 and 2002 were not made available. We thus categorized the study as having an unclear risk of bias with regards to assessment of exposure.

The outcome measure in Fritschi et al. included mortality (deaths) which are recorded after initiation of study.[17] We had therefore classified the study as having low risk bias in this domain (absence of outcome at start).

Certain plausible prognostic variables such as sex and 5-year age group were identified for standardization purposes in Fritschi et al.[17] However, there was no mention of other potential prognostic variables such as smoking status and exposure to other carcinogens, for instance asbestos and hence we classify the study as having unclear risk of bias.

Fritschi et al. reported the use of standardization performed for certain plausible prognostic variables only such as sex, 5-year age group and calendar year.[17] However, adjustment was performed for only some of the plausible prognostic variables and hence we classified the study as having uncertain risk of bias.

In Fritschi et al. the outcomes comprised of mortality which were recorded according to specific causes of deaths.[17] We thus categorized the study as having low risk of bias with regards to assessment of outcome.

The study had reported complete follow-up data where participants are made up of employees taken from the bauxite mines or alumina refineries.[17] We had therefore classified the study as having low risk bias in this domain.

We categorized the study as having unclear risk of presence of co-intervention bias as there was no mention of documentation of relevant co-interventions in the exposed and non-exposed.[17]

Exposure towards Bauxite and Alumina had no relationship with mortality of overall cancer (RR 0.93, 95% CI 0.62 to 1.41; Fig. 2 and Table 2).

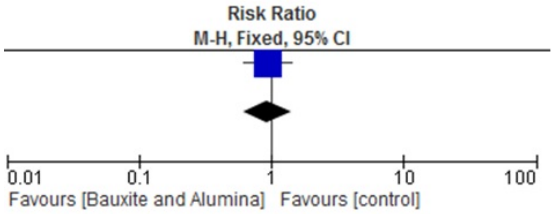

Figure 2. Forest Plot – Mortality of overall cancer among those exposed to Bauxite and Alumina versus non-exposure

There was no association between exposure towards Bauxite and Alumina with mortality of any of the specific cancers measured - colorectal cancer (RR 0.66, 95% CI 0.26 to 1.70; Table 2); prostate cancer (RR 1.00, 95% CI 0.11 to 8.91); bladder cancer (RR 0.75, 95% CI 0.08 to 7.18); kidney cancer (RR 0.75, 95% CI 0.08 to 7.18); trachea, bronchus and lung cancer (RR 0.85, 95% CI 0.42 to 1.71); pleura, mesothelioma (RR 0.62, 95% CI 0.12 to 3.21); melanoma (RR 2.74, 95% CI 0.15 to 49.57).

Table 2. Mortality of cancer, circulatory disorders, respiratory disorders and injury among those exposed to Bauxite and Alumina versus non-exposure

	Bauxite and Alumina		Control			Risk Ratio M-H,Fixed, 95% CI	Test for Overall Effect, Z	P value
	Events	Total	Events	Total	Weight			
Overall Cancer								
Fritschi 2008	105	5770	28	1438	100.00%	0.93 [0.62, 1.41]		
Total (95% CI)		5770		1438	100.00%	0.93 [0.62, 1.41]	0.32	0.75
Colorectal cancer								
Fritschi 2008	16	5770	6	1438	100.00%	0.66 [0.26, 1.70]		
Total (95% CI)		5770		1438	100.00%	0.66 [0.26, 1.70]	0.86	0.39
Prostate cancer								
Fritschi 2008	4	5770	1	1438	100.00%	1.00 [0.11, 8.91]		
Total (95% CI)		5770		1438	100.00%	1.00 [0.11, 8.91]	0.00	1.00
Bladder cancer								
Fritschi 2008	3	5770	1	1438	100.00%	0.75 [0.08, 7.18]		
Total (95% CI)		5770		1438	100.00%	0.75 [0.08, 7.18]	0.25	0.80
Kidney cancer								
Fritschi 2008	3	5770	1	1438	100.00%	0.75 [0.08, 7.18]		
Total (95% CI)		5770		1438	100.00%	0.75 [0.08, 7.18]	0.25	0.80
Trachea, bronchus, lung cancer								
Fritschi 2008	34	5770	10	1438	100.00%	0.85 [0.42, 1.71]		
Total (95% CI)		5770		1438	100.00%	0.85 [0.42, 1.71]	0.46	0.64
Pleura, mesothelioma								
Fritschi 2008	5	5770	2	1438	100.00%	0.62 [0.12, 3.21]		
Total (95% CI)		5770		1438	100.00%	0.62 [0.12, 3.21]	0.57	0.57
Melanoma								
Fritschi 2008	5	5770	0	1438	100.00%	2.74 [0.15, 49.57]		
Total (95% CI)		5770		1438	100.00%	2.74 [0.15, 49.57]	0.68	0.49

Table 3 illustrated the quality of evidence for the main selected outcomes by using the GRADE approach which took into consideration the following parameters - the methodological design, the limitations as measured by the risk of bias, the inconsistency, the indirectness, the imprecision and the risk of publication bias to assess the quality of the body of evidence for the main outcomes. GRADE Working Group grades of evidence graded the outcomes (overall cancer, overall circulatory, overall respiratory and overall injury) as moderate in quality.

DISCUSSION

We noted that exposure towards bauxite and alumina did not have an effect on mortality due to overall cancers. In addition, exposure towards these metals did not have an effect on mortality due to specific cancers such as colorectal cancer, prostate cancer, bladder cancer and kidney cancer. Mortality due to other forms of cancer such as trachea, bronchus, lung cancer, pleura cancer, mesothelioma and melanoma, mesothelioma and melanoma were all noted not to have any changes in risk ratios towards bauxite and alumina. Friesen et al. in fact noted that cumulative inhalable alumina and bauxite exposure did not appear to increase the risk of incident cancers; however, exposure to these compounds may lead to an increased risk of non-malignant respiratory diseases.[11]

The development of these forms of cancer among miners noted in this review may occur as a result of exposure to other physical hazards present in mines and refineries. For instance, sun exposure may well have initiated development of skin cancer such as basal cell carcinoma, squamous cell carcinoma and melanoma among these workers.[19] Taeger et al. in a pool analysis of population-based studies found that lung cancer is higher in miners and quarrymen.[20]

Aluminium workers acquired these particles via fumes as well as inhalation of particles (aerodynamic diameter ≤ 100 µm), thoracic fraction (< 28 µm), and respirable fraction (< 10 µm).[21] Exposure to Aluminium occurs among individuals engaged in the process of Aluminium cutting, filing and welding as well as in humans living in those environments.[22] More studies should be done to study the incidence of morbidity and mortality due to cancers in these individuals exposed for a longer duration of time. The articles did not mention whether these patients were screened early to

Table 3. Summary of findings for the main comparisons

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bauxite and Alumina exposure versus Non-exposure	Control	Relative (95% CI)	Absolute	
Overall cancer (follow-up mean 10 patient-years)											
1	observational studies	no serious limitations	no serious inconsistency1	no serious indirectness1	no serious imprecision	increased effect for RR ~11	105/5770 (1.8%)	28/1438 (1.9%)	RR 0.93 (0.62 to 1.41)	1 fewer per 1000 (from 7 fewer to 8 more)	~~⊖⊖⊖~~O MODERATE
								2%		1 fewer per 1000 (from 8 fewer to 8 more)	
Overall circulatory (follow-up mean 10 patient-years)											
1	observational studies	no serious limitations	no serious inconsistency1	no serious indirectness1	no serious imprecision	increased effect for RR ~11	80/5770 (1.4%)	15/1438 (1%)	RR 1.33 (0.77 to 2.3)	3 more per 1000 (from 2 fewer to 14 more)	~~⊖⊖⊖~~O MODERATE
								1%		3 more per 1000 (from 2 fewer to 13 more)	
Overall respiratory (follow-up mean 10 patient-years)											
1	observational studies	no serious limitations	no serious inconsistency1	no serious indirectness1	no serious imprecision	increased effect for RR ~11	7/5770 (0.1%)	0/1438 (0%)	RR 3.74 (0.21 to 65.45)	-	~~⊖⊖⊖~~O MODERATE
								0%			
Overall injury (follow-up mean 10 patient-years)											
1	observational studies	no serious limitations	no serious inconsistency1	no serious indirectness1	no serious imprecision	increased effect for RR ~11	43/5770 (0.7%)	8/1438 (0.6%)	RR 1.34 (0.63 to 2.84)	2 more per 1000 (from 2 fewer to 10 more)	~~⊖⊖⊖~~O MODERATE
								0.6%		2 more per 1000 (from 2 fewer to 11 more)	

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate

detect the presence of Cancer and early intervention and treatment given to prevent mortality. Lung cancer survival has improved with early detection and screening with targeted treatment and immunotherapy.[23]

Lung and bladder cancers have been reported in Soderberg operation workers in Aluminium industries from some countries only but not for cancers in other sites such as stomach, pancreas, brain prostate and lymphatics.[24] These studies did not mention about the mortality of the cancer patients.

We hope that this systematic review which was done using current available evidence of hazards of Bauxite mining with mortality due to cancer will be used as a guide for stakeholders and legislators to settle the issues of bauxite and aluminium mining.

Although the number of trials is small, we conclude that the exposure to bauxite and alumina was not associated with differences in mortality due to overall cancer and specific types of cancer. The findings of this review concur with the decision made by the U.S. Environmental Protection Agency (EPA) to not classify aluminium or its compounds for human carcinogenicity25 and also with the American Conference of Governmental Industrial Hygienists (ACGIH) which has designated aluminium and its compounds as a group A4 substance - "not classifiable as to human carcinogenicity".[25,26]

We observed that the trial evidence was generally of good quality with a low risk of bias. We identified seven records but excluded six as they did not fulfill our inclusion criteria. The employees had the same point of origin and

all completed the study. Mortalities due to cancer were the outcomes measured.

The trial did not show differences in mortality of cancer due to exposure to Alumina and Bauxite. Potential biases such as the job history, prognostic variables and co-interventions were not mentioned during the review process.

We are unaware of similar reviews covering this topic for us to agree or disagree with other studies or reviews.

Strengths and limitations of this study

This is the first systematic review on incidence of cancer mortality as a result of exposure towards alumina and bauxite.

The strengths of this review included focusing only on the most definitive of observational study designs which were cohort studies, using appropriate search engines for identification of studies and applying relevant risk of bias for the included studies.

Though extensive search was made, the literature was language restricted to English. We hope to see more individual cohort studies performed globally on alumina and bauxite which would further increase the number of included studies in future meta-analyses.

CONCLUSION

There is no evidence to show that exposure to bauxite and alumina will cause an increase in mortality due to of overall cancer and specific types of cancer.

Initial results show that there is no association between bauxite and alumina exposure with increase in mortality of overall cancer, and other specific types of cancer such as cancer of lip, cancer of the oral cavity and pharynx, cancer of digestive organs, cancer of respiratory and intrathoracic cancer, melanoma, mesothelioma, cancer of male genital organs, urinary tract cancer, cancer of brain and central nervous system, cancer of thyroid, endocrine cancer, leukaemia and lymphomas.

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