

# Is Exposure to Titanium Dioxide Nanoparticle Associated with Occupational Lung Cancer among Titanium Dioxide Production Workers? An Emerging Issue

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## Abstract

This systemic literature review was conducted to find out if there was an association between exposure to TiO<sub>2</sub> NP (Titanium dioxide nanoparticle) and occupational lung cancer among TiO<sub>2</sub> production workers. An electronic database search was employed which generated several studies relating to TiO<sub>2</sub> nanoparticle toxicity. From these studies only ten (10) articles were chosen for this study because they met the review criteria. Two articles were centered around cohort study design while other 8 studies were on experimental design. The two cohort studies did answer the review question that showed no association of TiO<sub>2</sub> toxicity and respiratory diseases while the experimental design studies produced conflicting results. The conflicting results were attributed to their objective, sample size, and the study designs. Despite the different conclusions there is adequate evidence in the experimental studies that demonstrated evidence of TiO<sub>2</sub> nanoparticle toxicity. Notable cases include cytotoxicity, genotoxicity, apoptotic and cell necrosis in rat and human cells exposed to TiO<sub>2</sub> which is generally dose response related. The strengths and limitations of the 10 studies are also discussed. General understanding gained from these studies is for appropriate agencies to be proactive in developing mitigation and controls measures against nanoparticle exposure. This is necessary to avert repetition of previous experiences with exposure to asbestos fibers as a point of reference.

## Keywords

Titanium Dioxide, Nanoparticles, Lung Cancer, Toxicity

## 1. Introduction

Richard Feynman a University Professor in 1959 proposed the idea of nanotechnology engineering [1]. “There’s plenty of room at the bottom” was Richard’s famous quote relating to the concept of working with nanoscopic materials of sizes ranging from 0.1 - 100 nm [2]. Nanotechnology is a rapidly developing industry throughout the world since the idea proposed by Richard. This engineering discovery has brought about medical, engineering, and economic prosperity to most industrialised countries. For example, some industrial paints, food, computer chips, and sunscreens are manufactured from nanomaterial [3]. It is the physicochemical properties of nanomaterial that makes them very economical because of their large surface area, structure, solubility, super strength than steel and an excellent conductor of electricity [4].

The scientific triumph has also brought with it emerging health concerns according to most literatures. This is a concern within occupational health setting where manufacturers involved in the production of nano engineered products may be exposed to nano dusts and particles [5]. In addition, nanomaterial is widespread throughout the world presenting new challenges to risk assessment managers to find solutions to control risks and hazards associated with the use of Carbon Nano Tubes and nanomaterial.

This review is focused on Titanium dioxide nano particle that is widely used to manufacture colour in paint products, plastics, papers, inks, food colour, toothpaste, and skin products [6]. The nano particle has been known to cause inflammation through entering a biological system through dermal; ingestion; and inhalation pathway. Moreover, Titanium dioxide nanoparticle is known to cause lung inflammation and the particle can also redistribute from the lung to kidney, liver, and brain and it is closely associated with ROS (Reactive Oxygen Species) [7]. Moreover, Titanium dioxide nanoparticle has been shown to induce ROS in mitochondria leading to DNA damage in lung cells.

Titanium dioxide Nano particle comes in three forms which include Rutile (mineral form), Anatase (Mineral and crystal form); and Brookite. Anatase form of  $\text{TiO}_2$  NP is the most reactive form known to cause inflammation to lung of laboratory rats than Rutile and Brookite, however,  $\text{TiO}_2$  NP normally exist in both forms in general [8].

## 2. Methods

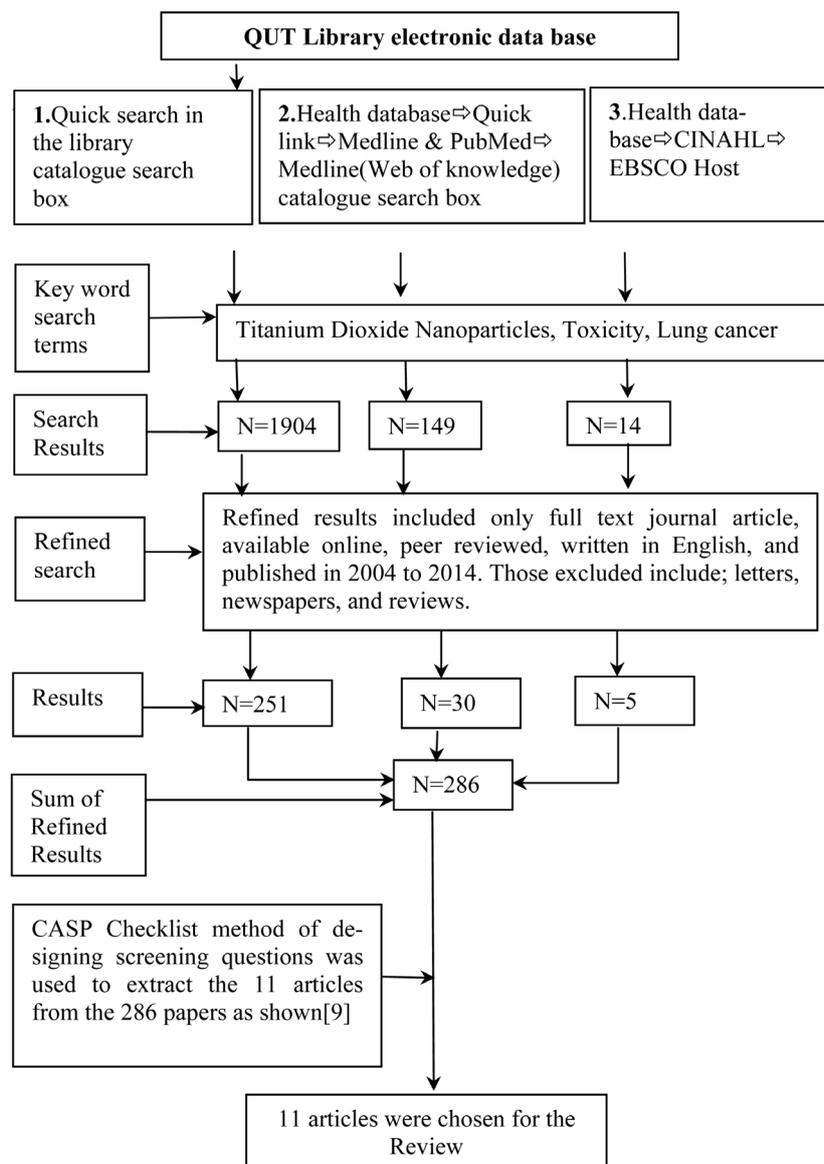
The research question for this systematic literature review was constructed using Cochrane “PICO” method. Since there is lack of long term epidemiological study design using cohort based studies from human exposure it is difficult to formulate research question using intervention type questions. Therefore, only “P” and “O” from PICO were used to construct the question. That is to design the review question using Population that is affected from exposure to a disease as the outcome. This approach is recommended by Cochrane Library Tutorial.

## 2.1. Literature Search Strategy

After the research question was formulated a search was conducted using QUT Library electronic data base. The search was conducted on the 11, April 2014 using the quick search box as shown in the 1<sup>st</sup> box of **Figure 1**. The 2nd lot of search was done on the 14th of April 2014 using the health data base and narrowing the search to Medline and Medline Web of knowledge. The same search engine was used for the 3rd link which led to EBSCO host as shown in the 3rd box of **Figure 1**.

## 2.2. Key Search Terms

The keywords used in this order include Titanium dioxide nanoparticles lung cancer toxicity. In the first quick search button the following strategy was used



**Figure 1.** Shows how the Systematic Literature search was done.

as noted, “Titanium dioxide nanoparticle” AND “Lung cancer” was entered resulting in 1904 papers as indicated in **Figure 1**.

As with the other two data base searches the keywords were entered without open and closing inverted comas resulting in 149 papers for Medline Web of knowledge link and 14 papers for EBSCO host.

### 2.3. Refined Search

The search was refined to extract only research papers that has the following attributes which include only full text papers, journal format, available online, peer reviewed, and only in English language, and papers published within 2004-2014. The reason for choosing articles within this period is to gain the latest information on Titanium dioxide nanoparticle toxicity. The articles that were excluded are papers that do not have key word search terms, newspapers, reviews and letters. It is also worth noting that the contents of the papers were screened and those not related to the research question were eliminated. Moreover, only primary sources were included while secondary sources were not considered. The search results from the refined strategy yielded a sum of 286 articles from the three search data bases.

### 2.4. CASP (Critical Appraisal Skills Programme) Method

CASP [9] was employed to scrutinise the remaining 286 articles to obtain papers that met the criteria for the research question. The reason for further scrutiny is to ensure that only quality research papers were extracted, being valid, with results being statistically significant, and the outcome of the papers did answer the research question to prevent biases.

Refer to **Figure 1** for explanation on methods used to select articles for the review.

#### 2.4.1. Filtering Questions

The following questions were used to extract quality papers from the 286 papers. The values assigned to each question asked are;

YES = 1, Unsure = 0.5, and No relevance = 0

##### 1. IS IT A TRUST WORTHY STUDY?

- 1) Was the objective of the study explicitly explained?
- 2) Were indicators/interventions explicitly described?
- 3) Is the research design relevant for human toxicity studies?
- 4) Is the sample size and sample reflective of the population?
- 5) Are confounding variables stated in the study that may affect the results?
- 6) Was pathogenesis described clearly in the study?
- 7) Was aetiology and prognosis clearly described in the study?
- 8) Was objective measurement conducted to minimise bias?

##### 2. IS THE RESULT OF THE STUDY TRUST WORTHY?

- 9) Are the tests results reproduce able in the next experiment?
- 10) Are the results statistically significant?

### 3. IS THE STUDY OUTCOME BENEFICIAL TO THE SOCIETY?

- 11) Are the test results relevant to human exposure?
- 12) Will the results contribute to new knowledge of nanoparticle toxicity studies?
- 13) Will the results assist in mitigating nanoparticle hazard and risks within workplace setting?
- 14) Are the results conclusive?

#### 2.4.2. Assessing Quality Papers Based on CASP Method

**Table 1** below shows how quality papers were selected following the CASP method guided by the above fourteen (14) questions with ratings of 0 to 1; 1 representing YES, there is relevance, 0.5 being for UNSURE and 0 for NO RELEVANCE to the study.

#### 2.4.3. Author's Total Scores Based on the Fourteen Filtering Questions Asked

As shown in **Figure 2** three (N = 3) of the papers reviewed had the highest score of fourteen (14) out of 14 questions, four (N = 4) of the papers had a higher score of 12 - 13 out of 14 questions, three (N = 3) papers had a high score of 11 - 11.5 out of 14 questions meeting the quality screening test using the CASP method to be selected for our review. Only one (N = 1) paper with a score of 7.5 was selected for the review because of interesting results.

## 3. Results

A total of eleven (N = 11) articles were selected for the review based on the paper

**Table 1.** Shows Ratings for each paper based on 14 filtering questions.

Journal article	CASP Screening questions (1 - 14) with assigned values													
	0 = No Relevance; 0.5 = Unsure; 1 = Yes, there is relevance													
Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Ambalavanan <i>et al.</i> 2013	0.5	1	1	0.5	0.5	1	1	1	0.5	0.5	1	1	1	0.5
Belade <i>et al.</i> 2012	1	0	0.5	0	0	0.5	0.5	0	0.5	1	1	0.5	1	1
Boffetta <i>et al.</i> 2004	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ellis <i>et al.</i> 2010	1	1	1	1	1	1	1	1	1	0.5	1	1	1	0.5
Grassian <i>et al.</i> 2007	1	1	1	0.5	0.5	1	1	1	0.5	1	1	1	1	1
Lai <i>et al.</i> 2008	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ling <i>et al.</i> 2011	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Naya <i>et al.</i> 2012	1	0.5	1	0.5	1	1	1	0.5	0.5	0.5	1	1	1	1
Osman <i>et al.</i> 2010	0.5	1	1	0.5	0.5	1	1	1	1	1	1	1	1	0.5
Srivastava <i>et al.</i> 2012	1	0.5	1	0.5	0.5	1	1	0.5	0.5	1	1	1	1	1
Zhang <i>et al.</i> 2013	0.5	0.5	1	0.5	0.5	1	1	1	1	1	1	1	1	1

As shown in **Table 1** Eleven (N = 11) papers were screened based on the fourteen filtering questions asked and were each given a score of 0 to 1 to determine their overall score.

selection criteria as indicated.

As shown in **Table 2** results from both cohort studies on occupationally exposed workers to titanium dioxide workers revealed no significant risk from carcinogenic induced respiratory diseases. The mathematical modelling based study

**Table 2.** Showing summary of the findings in the eleven (11) studies.

Study	Design	Research question	Sample	Measures	Results
Boffetta <i>et al.</i> , 2004	Cohort Study	Is lung cancer mortality related to occupational exposure to TiO <sub>2</sub> NP?	Follow up study on 15,017 workers (14,331 men) in Europe 686 were females	Study on exposed workers in 11 TiO <sub>2</sub> factories in six European Countries to assess mortality and carcinogenicity effects.	There is no carcinogenicity effect to exposed TiO <sub>2</sub> NP workers. The result is statistically significant
Ellis <i>et al.</i> , 2010	Cohort Study	Is there an increase in mortality among workers of three Titanium dioxide plants in the United States?	A total of 5054 individuals were sampled at 3 DuPont TiO <sub>2</sub> Plants for over a 40-year period	The mortality experience of the TiO <sub>2</sub> process workers were compared with the US population during follow up	There are no significant increases in the mortality in the cohort relating to TiO <sub>2</sub> exposure which is low compared to US population.
Ling <i>et al.</i> , 2011	Mathematical simulation of TiO <sub>2</sub> exposure	Is there an exposure risk to TiO <sub>2</sub> workers?	Review data from other studies to quantify risk exposure to TiO <sub>2</sub>	Applied risk modelling to quantity risk exposure to TiO <sub>2</sub> by workers	Uncertainty because not applied to real situation and admitted biasness in the design 3 experiments conducted were statistically significant (P < 0.05). Cell necrosis and apoptotic cells were evident which is dose response dependent.
Lai <i>et al.</i> , 2008	Experimental - in vitro tests	Does TiO <sub>2</sub> NP exert differential cytotoxic effects on various human cell types?	3 different experiments conducted repeatedly 3 times on human neural cells and fibroblasts.	Cells were exposed to TiO <sub>2</sub> NP for cytotoxicity tests	Results not statistically significant. TiO <sub>2</sub> Anatase nanoparticle crystal forms are not geno toxic following in tracheal instillation in rats.
Naya <i>et al.</i> , 2012	Experimental In vivo tests	Is there toxicity of TiO <sub>2</sub> through inhalation exposure pathways?	64 male Sprague Dawley rats (7 wks. old) were used	Single instillation of TiO <sub>2</sub> intratracheal, orally, at 1.0 or 5.0 mg/kg body weight and 0.2 or 1	Cytotoxicity and geno toxicity to TiO <sub>2</sub> NP were dose-response depended. Cells exposed were 2 times greater than un exposed cells to TiO <sub>2</sub> regarding geno toxicity.
Osman <i>et al.</i> , 2010	Experimental In vitro tests	Is there cytotoxicity and geno toxicity effects of TiO <sub>2</sub> NP to Hep-2 cells?	Human Cell cultures of Hep-2 Cell line	The cells were exposed to various concentrations of TiO <sub>2</sub> NP to observe geno toxicity and cytotoxicity effects	TiO <sub>2</sub> -NP exposed cells showed oxidative stress effects promoting ROS (Reactive Oxygen Species), and decrease in catalase and glutathione enzymatic activity. Apoptosis in cells was also observed.
Srivastava <i>et al.</i> , 2013	(Experimental) In vitro tests	Does TiO <sub>2</sub> NP induce oxidative stress and geno toxicity effects on HumanA549 lung cancer cells A549?	Human lung cancer cells HumanA549	To measure TiO <sub>2</sub> NP effect on apoptosis, oxidative stress and geno toxicity in human lung cancer cell.	Apoptosis in cells was also observed.
Zhang <i>et al.</i> , 2013	(Experimental) In vitro test method	Is there risk of cytotoxicity of mouse macrophages from exposure to various forms of TiO <sub>2</sub> NP?	Mouse Macrophages cells (Ana-1 and MH-S cells)	The cells were exposed to various forms of TiO <sub>2</sub> NP for cytotoxicity effects	Low toxicity in mouse macrophages cells & higher toxicity in Ana-1 cells than MH-S cells.
Grassian <i>et al.</i> , 2007	Experimental In vivo-mice whole body exposure 4 hrly	To assess the toxicity of TiO <sub>2</sub> to lung cells	6 weeks old male C57Bl/6 mice, well fed and weigh 22 and 25 g at the time of necropsy	In vivo-mice whole body exposure 4 hrly or sub acutely 4 hr/day for 10 days	Statistically significant to exposure. Mice exposed acutely to 0.77 - 7.22 mg/m <sup>3</sup> TiO <sub>2</sub> NP demonstrated minimal lung toxicity or inflammation at 0, 1 or 2 weeks after exposure.

## Continued

<b>Ambalavanan (Experimental)</b> <i>et al., 2013</i>	In vivo tests	<b>Will exposure to TiO<sub>2</sub> lead to lung inflammation and impairment of lung development?</b>	C57BL/6mice, 4 day old pups	<b>Intranasal instillation for distal pulmonary delivery, and exposed to TiO<sub>2</sub> Anatase 8 - 10 nm NP.</b>	<b>Single dose of TiO<sub>2</sub> nanoparticles caused cell inflammation. Multiple doses lead to increased inflammation and inhibit lung development.</b>
<b>Belade</b> <i>et al., 2012</i>	Experimental In vitro test method	Is there a difference in the cellular uptake of 3 different manufactured Nanoparticles (MNP) and TiO <sub>2</sub> in Human lung epithelial and fibroblast cells?	Human 16HBE bronchial epithelial cells and MRC5 fibroblasts	Transmission microscope was used to assess the cellular uptake of the 3 Manufactured Nanoparticles.	The 3 Nanoparticles was observed accumulated in the vesicles of cytosolic compartment and were absent from Mitochondria and nuclei. MNPs uptake in cells is a common phenomenon

provided uncertainties about the association between TiO<sub>2</sub> and respiratory induced malignant outcomes. While results from the 8 experimental studies done on rats showed no significant toxic risk from exposure to anatase nanoparticles while the results yield from the mice studies showed TiO<sub>2</sub> did cause cell inflammation with minimal lung toxicity. Interestingly, in the human cells studied there was positive association between TiO<sub>2</sub> with cytotoxicity and genotoxicity except the study by Belade *et al.* 2012.

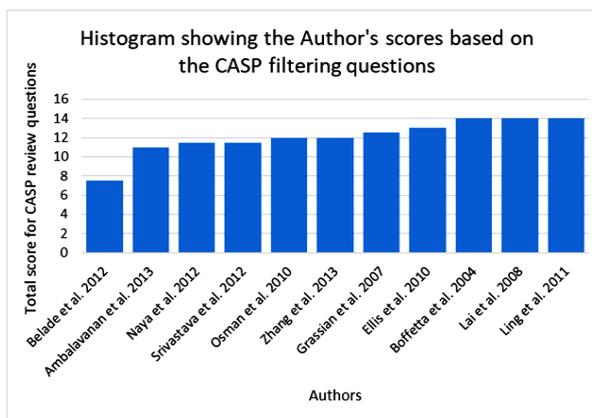
#### 4. Discussion

From the 11 papers that were extracted after the quality assessment the paper by Ling *et al.*, 2011 was omitted for analysis because the study was based on mathematical modelling extracted from other studies. The discussion will be based on **Table 2** page 7 - 9 including the summarized data based on the CASP screening questions on **Table 1** p. 6 and **Figure 2** p. 7.

##### 4.1. General Analysis

Out of the ten (N = 10) studies, two (N = 2) were cohort design studies while eight (N = 8) were experimental based studies. The two cohort studies were long term studies which required a follow up on the same subjects over a period of time after the initial study. This was necessary to establish if there was an association of mortality cases among TiO<sub>2</sub> processing workers exposed to TiO<sub>2</sub> dusts. The eight (8) experimental studies on the other hand employed biological modelling to make inferences based on their objectives. The experimental designs involve an array of tests to measure outcomes in cytotoxicity, genotoxicity, enzymatic activity, cell apoptosis, inflammation, and cellular oxidative phosphorylation as the main examples documented.

In general, the 10 studies presented conflicting conclusions and this is because of the various research designs, objectives, methods, type of sample chosen, sample size, and the type of end points the researchers were contemplating to achieve. The end points can include short term studies that relate to acute toxicity testing or long term studies involving chronicity testing for carcinogenicity



**Figure 2.** Shows the Authors and their score based on the-CASP 14 filtering questions.

tests. Most of the studies lacked properly designed research question, refer to **Table 2**.

A number of experimental studies developed more than one experiment to assess a certain phenomenon of interest like cytotoxicity, genotoxicity, and oxidative phosphorylation [10] [11] [12] [13] [14]. This was the case with Osman *et al.*, 2010 and Srivastava *et al.*, 2012. It was a challenging task to discuss each of these experiments therefore the discussion in this review will relate to the review question of these papers. In addition, the strengths and limitations of each paper will be discussed starting with the cohort studies by Boffeta *et al.*, 2004, Ellis *et al.*, 2010, and the experimental studies. The review will conclude with the limitations and concluding remarks.

#### 4.2. Observational and Cohort Study Design

The two cohort studies by Boffeta *et al.*, 2004, and Ellis *et al.*, 2010 are generally of high quality with inclusion of large sample sizes, sound methodology, and clear outcomes.

Cohort study design minimises selection bias as it is generally a long term study on certain groups of subjects that require follow up. Statistical precision of such studies will generally be significant having a P value of <0.05 or much higher example  $P < 0.001$  to determine the association between the exposure or non-exposure scenarios. In the context of this review the authors aim to ascertain the association between exposure to TiO<sub>2</sub> Nanoparticle and Lung cancer in TiO<sub>2</sub> processing plants workers. The two selected studies are relevant for this review as they clearly demonstrated in their outcomes that there was no association between malignant and non-malignant respiratory diseases. A narrative approach is taken to discuss the research results other than the use of statistical software which is a limitation of this review.

The studies by Ellis *et al.*, 2010 was conducted for a 29-year period studying workers exposed to TiO<sub>2</sub> process within three DuPont Plants in the USA. Ellis *et al.*, 2010 looked at employee's exposure to TiO<sub>2</sub> between 1935 when the three

Plants were constructed and in operation until 2006. It was not clearly established how the follow ups were done, however, it was documented by the authors that they obtained the records from those Plants where their subjects were employed. These involved gathering updated demographic records such as employment history, death certificates, record of termination from employment, age, and gender as some examples [15]. As for Boffetta *et al.*, 2004 their study looked at cohorts between 1959-1972 and 1997-2001.

As a result of the great length of follow up the outcome of their studies were conclusive. Interestingly, both studies presented similar results because their study design and sample size were similar. Furthermore, both authors admitted to confounding variables particularly noting smoking history of the workers with few cases of employees exposed to asbestos. Despite the confounding variables the outcome of the two studies showed no association between respiratory related diseases and TiO<sub>2</sub> dusts in processing Plants [16]. Although the results appear significant there could be room for selection bias, in terms of recruitment and responses elicited. For instance, Ellis *et al.*, 2010 admitted that they assumed all employees working in one of the three DuPont Plants to be Caucasians when there were no office records presented to them on the ethnicity of the subjects.

### 4.3. Experimental Study

In this study a total of 8 laboratory based experiments were done using biological systems in a controlled environment.

The biological model involved the use of rat cells, human cells, and whole animal body exposure for which certain toxicity studies can be done. The common toxicity studies include a control and a treated sample that were manipulated to achieve an outcome by the manipulator. Animal and human cells were exposed to TiO<sub>2</sub> nanoparticle at various concentrations, and exposure duration, with observance on endpoints. The methods employed for the tests involved *in vitro*, *in vivo*, and whole organism exposure tests. All the studies generated various conclusions and this depended on their study objectives, study design, and methodology that were used.

Experimental studies do have strengths and limitations just like any other study design. A key advantage is that Scientists can draw quick conclusions from causal inferences and incidence rates and several outcomes can be assessed in which similar experiments can be repeated. The sample size for the 8 toxicity studies were not clearly specified. It appears the sample sizes used were small and the results demonstrated as statistically significant by the authors can be false due to type1 error. For instance, a study by Ambalavanan *et al.*, 2014 only used 6 mice for the test and concluded that single dose of TiO<sub>2</sub> caused inflammation to the rat pups. This is similar to the experiment by Grassian *et al.*, 2007 who used 6x 6 week old mice for whole body exposure. As one of the key limitations of experimental studies, generalizability of the results may have been done hence showing the results to be significant [17].

Moreover, due to stringent ethical conditions scientific experiments can be easily conducted using other methods such as *in vivo* and *in vitro* methods using bio assays. This is necessary to extrapolate results in the experimental model to make inferences to human subjects. In this context the cell toxicity results in TiO<sub>2</sub> exposure can be extrapolated to human exposure situations within workplace settings. The limitations of the 8 experiments with reference to the review question of this paper are that the sample sizes used were not well defined and appear to be small which could have led to generalization of results. Moreover, Titanium dioxide nanoparticle is already confirmed by IARC as group 2B carcinogen due to toxicity evidence from experimental studies. This is a signal for appropriate Agencies throughout the world to utilize the available data and be proactive in instigating control measures to prevent similar experiences with Asbestos like cancer as a point of reference.

#### 4.4. Limitations

This review has limitations due to the following points. Firstly, it has not searched other data bases around the world to provide adequate data for the review. If other data bases were explored the results presented here may be different.

Secondly, only articles in English language were chosen restricting other articles that may present important findings in other languages. Thirdly, the experimental model results may not truly reflect the real exposure scenario of worker's exposure to TiO<sub>2</sub> nanoparticles in the working environment. This is attributed to interspecies differences and that the latency period for carcinogenicity is longer than acute toxicity studies as demonstrated in the experiments.

#### 5. Conclusion

The systematic review analysed the association between exposure to TiO<sub>2</sub> nanoparticle and lung cancer among TiO<sub>2</sub> processing workers. The literature search utilized the QUT Library electronic data base which identified several TiO<sub>2</sub> nanoparticle toxicity studies. From these studies only ten articles were extracted for analysis. Two articles out of the ten papers were cohort designed studies while the other eight were experimental designed studies. The two cohort studies revealed no association between respiratory related ailments and TiO<sub>2</sub> exposure therefore having answered the review question of this paper. Although, the eight experimental studies demonstrated varying conclusions they applied common methodologies such as in using biological modelling, and did identify routes of TiO<sub>2</sub> nanoparticle exposure as the agent for toxicity. Moreover, a number of the experimental studies have demonstrated cell toxicity in the form of cell necrosis, apoptotic manifestations and oxidative stress effects which were dose response dependent. These results reflect the likely exposure scenario to exposed workers in TiO<sub>2</sub> processing plants. Although less is known about the health risks associated with TiO<sub>2</sub> nanoparticle there is adequate evidence in animal and human

cell studies to be concerned with which require appropriate Authorities to be proactive in developing risk mitigation controls against unnecessary exposure to TiO<sub>2</sub> nanoparticle.

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