*Department of Environment and Geography*

*University of York*

# Assessment Submission Cover Sheet 2018/19

***This cover sheet should be the first page of your assessment***

| | |
|---|---|
| **Exam Number:** Y3864317 | **Module Code:** ENV00021M |
| **Module Title:** Environment & Health | **Assessment Deadline:** 7th March 2019 |

**I confirm that I have**

- **conformed with University regulations on academic integrity**
- **please insert word count** 3119
- **not written my name anywhere in the assessment**
- **checked that I am submitting the correct and final version of my coursework**
- **saved my assessment in the correct format**
- **formatted my assessment in line with departmental guidelines**
    - I have ensured my work is compatible with black and white printing
    - I have ensured the compatibility of any graphs or charts included in my submission
    - I have used 12pt font (preferably Arial or similar)
    - I have ensured all pages are clearly numbered using the system 1 of 6, 2 of 6 etc. Page 1 will be your Assessment Submission Cover Sheet
    - I have ensured my examination number is on every page of the assessment

**PLEASE TICK BOX TO CONFIRM**

V

**Please note: if you have any questions please refer to the FAQs available on the VLE (Student Admin Hub).**

# Assessing the extent of growth restriction from pre-natal & neo-natal exposure to nitrogen fertilisers in china- Does exposure to nitrogen fertilisers pose as a health risk?

## 1. INTRODUCTION

The use of synthetic and inorganic fertilisers has rapidly increased since the 1960's, with forecasts showing that the use of fertilisers is set to increase by up to 50% in future years (Sutton *et al.,* 2013). Fertilisers are widely used as they are an inexpensive method that enables plant and soil nutrients to be increased, which in turn leads to increase in crop productivity (Ward, 2009).

Despite the excessive use of fertilisers, there has been little research conducted on the adverse health effects relating to fertilisers and nitrogen inputs. Brief research has been conducted to assess the link between cancer and nitrogen inputs, and day to day effects such as irritation (Ward, 2009), however there has been little research on exposure to nitrogen fertilisers in general (Ward, 2009). There has also been a distinct lack of research regarding the different risk groups, with no research been conducted on the effect that excessive use of nitrogen inputs has on pre-natal exposure.

Due to the establishment of a knowledge gap, the aim of this study would be to establish whether pre-natal exposure to nitrogen inputs used in agriculture poses as a threat to health.

The objectives of the study would therefore be to:

a) Assess pre-natal and neo-natal exposure to nitrogen fertilisers and the effect it has on newborns through health markers over a year long period.
b) Assess the different pre-natal and neo-natal exposure pathways over a year long period.
c) Assess if there is a correlation between pre-natal and neo-natal exposure to nitrogen fertilisers and markers for health effects in newborns.

# 2. LITERATURE REVIEW

## 2.1 FERTILISERS IN AGRICULTURE

Various organic and non-organic fertilisers are used on a global scale in an attempt to improve efficiency and crop quality, howver with this increased use of fertilisers comes global environmental consequences (Savci, 2012). Non-organic fertilisers used for agricultural purposes usually contain phosphate, nitrate and ammonium, but because of the excessive use of fertilizers these chemicals accumulate therefore causing pollution. There are various consequences that arise from applying excessive amounts of fertilisers, including increases of nitrate and phosphate in drinking waters, and harmful levels of nitrogen in plants (Sonmez *et al.,* 2007). Nitrogenous fertilisers can have significant effects on underground and surface water, as a large proportion of the fertilizer applied to crops is not absorbed by the plant (Savci, 2012; Bryan & Hord, 2010). The most important consequence to water that occurs from excessive fertiliser use is water eutrophication, which increases aquatic plants and algae but causes degradation of water quality, making it unsuitable for drinking and for aquatic species (Rivers et al., 1996; Gross et al., 1998).

## 2.2 THE NITROGEN CYCLE

Many commercial fertilizers which are available to farmers contain plant available nitrogen in either the form of ammonium ($NH_4^+$), nitrate ($NO_3^-$) or urea (Shober, 2015). Although nitrogen inputs can be beneficial to crop yields if used correctly they can also be harmful to the environment if they are used excessively particularly in terms of water contamination.

The nitrogen cycle in agriculture is used to describe the inputs and losses that occur in farming. A typical rotation of grain crop starts with the plant residue that is left behind on the soils surface after harvest. Plant residue that is left behind provides source of organic matter and is incorporated into the soil through tillage. Organic matter is essential for plant growth and soil health as it contains forms of N that are not available to growing plants through the use of fertilisers. The N that is often unavailable to crops is made available through soil microorganisms which change the unavailable forms of N into forms that are plant-available. The Inorganic N is then taken up by the roots of the next growing crop in the rotation. The cycle repeats when this crop is harvested (See **Figure 1**). (Shober, 2015).

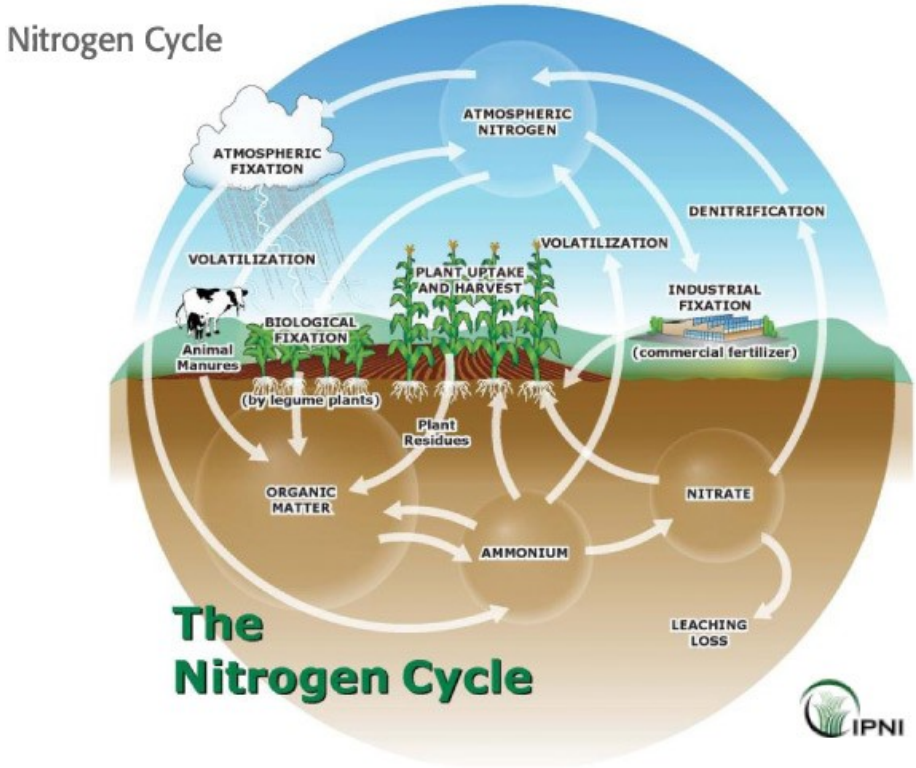


Figure 1. The Nitrogen Cycle. (Source: Shober, 2015).

## 2.3 EXPOSURE PATHWAYS OF FERTILISERS

Nitrogen inputs used for agriculture can enter the human body through a number of pathways, with inputs such as nitrogen fertilizer been most commonly ingested through contaminated water supplies (Ward, 2009: Harter, 2009). Contaminated water supplies are often drank by livestock and inhabit fish, both of which are eaten by humans, thus allowing nitrogen to be ingested. It has also been observed that the extensive use of fertilisers in agriculture, causes certain food items to contain levels of nitrate which a relatively high (Mensinga *et al.,* 2003; Bryan & Hord, 2010; Lundberg *et al.,* 2009). Other exposure pathways to be considered are inhalation, which is a particular concern to those who work in the production plants or on farms (Findlay, 2005). It could be said that women in developing countries are most at risk from ingesting nitrogen and thus adverse health effects, as there has been a recent shift in roles, with women now taking on the role of farmer (Kristjanson *et al*., 2011; O'Sullivan *et al.,* 2014) as the men are migrating to become involved in better paying jobs (Mehar *et al.,* 2012; Pretty et al., 2011). Those exposed to high levels of fertilisers through production and application during agriculture have often complained about eye, skin and nose irritations as well as nausea, headaches and respiratory issues (Cates, 2000).

## 2.4 KNOWN TOXICITY

As humans can be exposed to nitrogen fertilisers through a variety of pathways, it is important to understand the overall impact that this intake may have on human health. The U.S Environmental Protect Agency states that the reference dose for nitrate is 1.6 mg/kg$^{-1}$ body weight per day (Mensinga *et al*., 2003). To understand the effects that a dose of nitrate higher than the recommended reference dose can have, the Disability adjusted life years (DALYs) method can be used. DALYs is used to assess the number of years of life lost because of exposure to an environmental stressor, which essentially is measuring the overall impact of an environmental stressor in relation to health disruption with a study finding that the unintentional ingestion of chemicals such as those found in fertilisers caused 7,447,000 DALYs in 2004, most of which could have been avoided (Prüss-Ustün *et al.,* 2011).

## 2.5 AGRICULTURE IN CHINA

China is the worlds leading consumer of fertilisers, with around 287kg/ha of fertilizer being used in china (FAO, 2009). The amount of fertiliser used equates to 30% of the globes fertiliser supply’s, which is then used on only 9% of the worlds cropland (Wu *et al.,* 2018). Although they have the highest use of fertiliser, there is a lack of efficient use, resulting in severe chemical losses, often leading to global pollution (Chen *et al.,* 2014; Gu *et al.,* 2015). Although the use of excessive fertilisers in China has proven beneficial in ensuring food security for their population of 1.3 billion, it is not without its consequences (Zhang *et al.,* 2015). This need for increase food production has resulted in severe degradation of water sources often resulting in eutrophication (Borda *et al.,* 2011) and nitrate contamination in groundwater (Haung *et al.,* 2011). Investigations have been conducted regarding the levels of nitrate present in water in agricultural regions, with results showing that nitrate levels exceeded the WHO drinking water standards (Chen *et al.,* 2009) of 10 mg/L for surface water and 20 mg/L for groundwater that is consumed as drinking water (Zhang *et al.,* 2015). Taking these nitrate concentrations into consideration it is important to assess the possible health effects, with particular focus on those in rural and agricultural regions, as around 75% of Chinas rural population drinks groundwater that is contaminated (Zhang *et al.,* 2015).

# 3. RESEARCH METHODOLOGY

To meet the objectives of this project which were set out previously, a cohort study will be applied. The methods which are going to be used in the proposed project are mainly epidemiology based, as epidemiology is "the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems" (WHO, n.d.). The variety of methods which can be applied have the potential to assess the growth of infants born to mothers who are living, working or located in populations which are local to poor water quality.

## 3.1 STUDY AREA

Previous research and studies has revealed that China has a large agricultural sector and are heavy users of nitrogen fertilizer. It has also been acknowledged that China has some of the poorest drinking water quality, which poses as a threat to human health. Therefore, hospital patients will be used to assess pre-natal exposure and health risks. The hospital will be selected based on the surrounding population and location, as a hospital that treats women who are from areas with poor water quality are more likely to have higher exposure to nitrogen fertilisers, than people who are located in areas which receive clean water supplies. Taking this into consideration the hospital should be located within a close proximity to agricultural areas.

## 3.2 SAMPLING DESIGN

To ensure that the project is beneficial to its field, sampling needs to be of a standard that ensures results will be found. Therefore, from the hospital selected, 200 samples from mothers aged between 18 to 45, and their singleton newborns are to be collected over a year long period, equating to 400 samples in total. This sample size has been selected as the hospital selected may not have as many births per year as other hospitals, so the number of samples needs to be of a suitable size for the population. Its important to remember that a sample size that is too small may not be able to show a desired difference, but a sample range that is too large makes the project too complex and expensive, both of which should be avoided when possible to research (Martínez-Mesa *et al*., 2014). The samples collected on the selected days will be random, however data collection may be based on whichever women has their newborn first within a certain time period of each day such, i.e. the first newborn delivered between the hours of 11:00 hours and 14:00 hours.

## 3.3 QUESTIONAIRES

To assess any factors that may influence nitrogen levels in the blood, all mothers on admission to hospital will be asked to complete a questionnaire to assess their lifestyle and medical history. The questionnaire will contain questions relating to socio-demographic factors including age, martial status, ethnicity and education, and medical history including any previous pregnancies and birth outcomes. The questionnaire will also be used to assess alcohol and tobacco use and their main source of water. A similar study that looked at arsenic exposure, followed a similar questionnaire style as it allowed for the study to assess if any other factors contributed to health effects (Farzan *et al.,* 2017).

## 3.4 MARKERS FOR HEALTH EFFECTS IN NEWBORNS

As one of the objectives of the proposed project is to assess the effect of pre-natal exposure to nitrogen fertilisers and the effect on newborns through health markers. A variety of health marker data needs to be collected from newborns from each hospital. Development of newborns can be assessed through weight, head circumference and length (Jokinen, 2002). By evaluating health markers in newborns, assessment can occur to see if newborns have suffered from growth restriction in the uterus as a result of exposure to adverse conditions such as nitrogen fertilisers (Kramer *et al.,* 1999). It is also important to assess the health markers of newborns as those that have been subject to growth restriction in the uterus, as in the early neonatal period they are more susceptible to health issues such as hypothermia, hypoglycemia, infection (Creasy *et* *al.,* 2004; Brodsky & Christou, 2004) and damage to cognitive function (Indredavik *et al.,* 2005).

Data will also be collected during the infants regular check ups to assess neo-natal exposure. By checking their height, weight and head circumference at 0, 3, 6 and 12 months, then a correct assessment of whether exposure to nitrogen fertilisers in the womb and from breast milk has effected growth.

## 3.5 ANALYSIS OF HUMAN TISSUE

To assess the potential pathways of pre-exposure for nitrogen fertilisers a variety of different tests should be carried out on the mothers and their newborn. The tests which will be applied in this project include analysis of breast milk, umbilical cord blood and maternal and newborn blood samples. Nitrogen concentrations are to be tested in breast milk and cord blood of the mothers and newborns, as it has been found that pregnant women who are exposed to chemicals may transfer them to their fetus via the placenta and through breast milk (Aylward *et al*., 2014; Mondal *et al*., 2012). Maternal blood samples are an important method of analysis, as this is the matrix of how exposure to nitrogen can be transferred to breast milk (Ettinger *et al*., 2013), therefore if there are elevated concentration levels of nitrogen in the blood then there is also likely to be elevated concentration levels of nitrogen in breast milk.

Maternal blood tests shall be taken on admission to hospital and umbilical cord blood tests should be taken immediately after birth, along with newborn blood. Blood samples from the infant and breast milk samples should also be collected before leaving the hospital, 3,6 and 12 months during regular check ups to assess whether nitrogen concentrations levels have changed. Other studies testing exposure to different chemicals including a study conducted by Ettinger *et al.,* (2013) have used similar methods that assess concentrations in blood over different time periods. An increase in nitrogen levels may occur if they are being breastfeed, particularly if the breast milk samples reveal high levels of nitrogen.

By sampling breast milk, umbilical cord blood and maternal and newborn blood, it will allow for this project to assess whether some women have higher exposure rates and are therefore a threat to their infant.

## 3.6 STATISTICAL TESTING

Once the nitrogen concentrations levels in the samples has been analysed in the laboratory, SPSS software will be used to apply a variety of different statistical tests. As the aim of the project proposed is to understand whether pre-natal and neo-natal exposure to nitrogen fertilisers through a variety of pathways can effect growth, it would be suitable to assess the correlation between growth and nitrogen levels in the blood. Correlation tests should also be completed between nitrogen in newborn blood against the nitrogen found in breast milk. This will be completed by fitting a multivariable linear regression model, which aims to estimate the association between the blood and breast milk. The study completed by Ettinger *et al.,* (2013) used similar statistical testing to see if the variation in infant blood levels could be explained by the concentrations of lead in breast milk. The multivariable linear regression model could also be used to estimate the association between growth and concentrations of nitrogen in the blood.

To follow up the multivariable linear regression models, growth, blood concentrations, and breast milk concentrations will all be tested using spearman's rank to assess if any correlation between these variables is found (Mcdonald, 2014). In addition to this a chi-squared test may be conducted to show any associations between growth and the exposure method. As the project goes on other statistical tests may be implemented.

## 3.7 ETHICAL REQUIREMENTS

The project is likely to collect data that is sensitive and personal, therefore all aspects of ethics should be considered. Firstly, the project will have to comply with the terms and conditions set out by the University panels and the association that is funding the project. Secondly, hospitals in China need to be approached to discuss their ethical requirements. Requirements in China may be different to those in the UK, however the project will follow the necessary requirements, even if it means adjusting certain aspects of the project. Protocol may include questionnaires and consent forms being reviewed by human studies research ethics committees. Finally, patient and parental consent should be received to allow for any testing and blood samples to be taken, as well as taking all the precautions necessary to ensure that data is kept confidential.

Guidance on how to keep patient information confidential should be sought from the university panel and outside governing bodies.

Throughout the project all aspects will follow the regulations and agreements set out to ensure that there is no breach in the ethics particularly when sensitive information is involved.

## 4. SCOPE & LIMITATIONS

There is a current gap regarding the effects that excess nitrogen from fertilisers in the environment has on human health (Ward, 2009), particularly infants who are often more susceptible to illness due to their weak immune systems. There is a particular concern for populations from agricultural areas, with the population living in these areas being at risk from high exposure rates, particularly as they are likely to be drinking from potentially contaminated water (Ward, 2009). Due to these concerns, along with the concerns that drinking water is likely to contribute to the most common pathway of nitrate exposure (Chilvers *et al.,* 1984) further research is needed to allow for health effects of nitrate to be assessed. The proposed project will have the potential to be an important study to further assess the potential effects of nitrogen in infants due to pre-natal and neo-natal exposure. The research from the proposed project will be beneficial for assessing whether there should be major concern regarding exposure to nitrogen fertilizers, as well as providing the data needed to assess which areas of China are at risk.

Although the proposed project has several potential aspects that could be beneficial to the field of research, there are also several limitations to the project. Such limitations include the ability to access a substantial number of women who have come from agricultural areas, particularly when the sampling is only occurring over a year long period. This has the potential for only a certain number of women been exposed to agricultural circumstances. Due to this there could be an inaccurate spread of data, resulting in an incorrect assumption being made.

Another limitation with the project is that health markers are only been registered over a 12-month period. This provides the issue that an effect on health markers may not be seen until a later stage of life. Many studies have completed similar sampling over a 5-year period, to assess the effects that it may have on infants at a later stage. There is also no telling whether the exposure has had any neurological or respiratory effects, which could have been measured if the project focused on exposure in children.

Follow up health marker samples and blood samples may also be difficult to obtain, as mothers may not return for regular check ups.

Although there are a couple of limitations there is still the potential for the project to provide some beneficial information to researchers regarding nitrogen exposure.

## 5. PLAN OF WORK

Due to the nature of the project the estimated timeframe for completion of this project is 3 and a half years, however this may be subject to change. It is hoped that sampling will occur in a 2 -year period starting from July 2019 and ending in June 2021. This is subject to all sampling running efficiently. A Gantt chart (**Figure 2**) has been created to show the plan of work and time schedule for the proposed project.

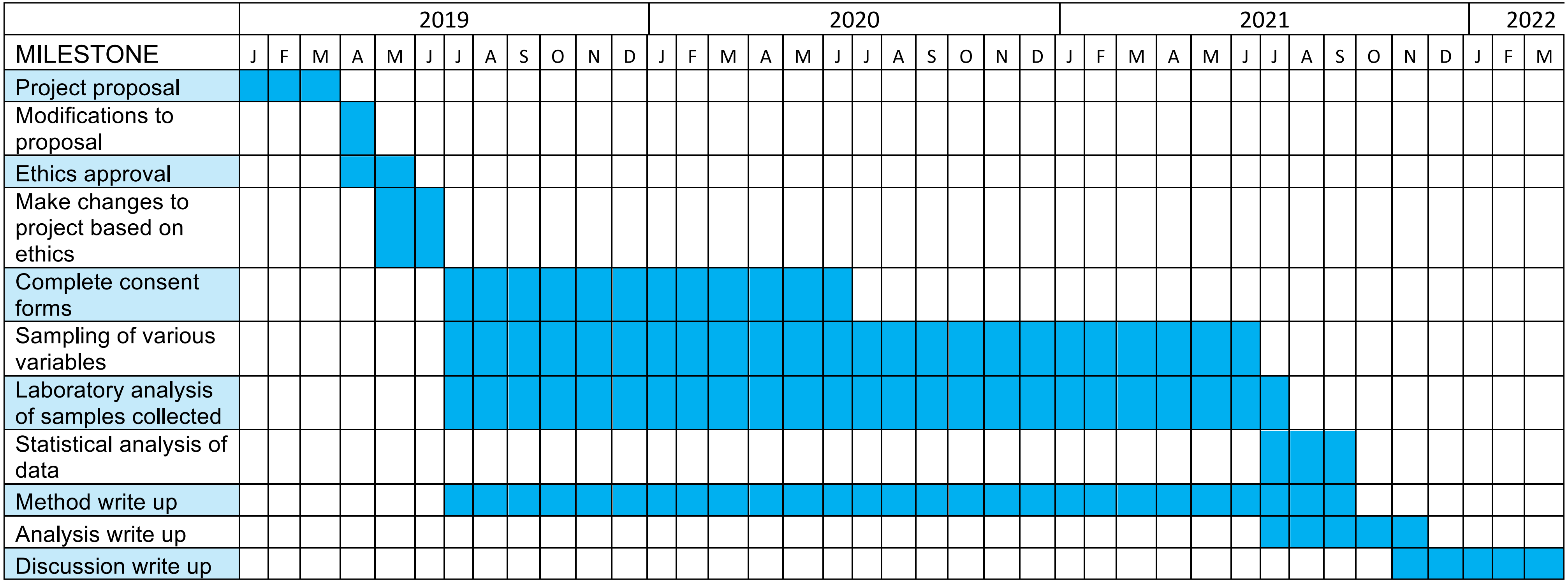


**Figure 2. Gantt chart of the time schedule for the proposed project starting in January 2019 and ending in April 2022**

Word count: 3119

## REFERENCES


Aylward, L.L., Hays, S.M., Kirman, C.R., Marchitti, S.A., Kenneke, J.F., English, C., Mattison, D.R. & Becker, R.A. (2014) Relationships of chemical concentrations in maternal and cord blood: a review of available data. *Journal of Toxicology and Environmental Health Part B*, **17**, pp.175–203. Doi: https://doi.org/10.1080/10937404.2014.884956

Borda, T., Celi, L., Zavattaro, L., Sacco, D. & Barberis, E. (2011). Effect of Agronomic Management on Risk of Suspended Solids and Phosphorus Losses from Soil to Waters. *Journal of Soils and Sediments*, **11**, pp.440-451.

Brodsky, D. & Christou, H. (2004) Current concepts in intrauterine growth restriction. *Journal of Intensive Care Medicine*, **19(6),** pp.307–319. doi: https://doi.org/10.1177/0885066604269663

Bryan, N.S & N.G. Hord, (2010). Dietary nitrates and nitrites: the physiological context for potential health benefits. In Food, Nutrition and the Nitric Oxide Pathway: Biochemistry and Bioactivity, Ed., Bryan, N.S. Houston, DESTech Publications, Inc., pp: 59-77.

Cates, J. (2000). Trees on drugs. *Watershed Sentinel*.

Chen, S.F, Li, W., Hu, K. L., Wu, W. L., Chu, Z. H. & Mao, W.F. (2009). Gis-Based Analysis of Spatio-Temporal Variability of Groundwater Nitrate Concentration in High-Yield Region in North China Plain. *Environmental Science*, **30**, pp.3541-3547

Chen, Y. J., Yang, J. Y. & Na, F.L. (2014). Analysis of Soil Environmental Quality Status of Arable Land in China. *Journal of Agricultural Science and Technology*, **16**, pp.14-18.

Chilvers, C., Inskip, H., Caygill, C., Bartholomew, B., Fraser, P. & Hill, M. (1984). A survey of dietary nitrate in well-water users. *International Journal of Epidemiology,* **13(3),** pp.324–331.

Creasy, R., Resnick, R.& Iams, J. (2004). Maternal fetal medicine. 5th ed. Maternal-Fetal Medicine: Principles and Practice.

Ettinger, A. S., Roy, A., Amarasiriwardena, C. J., Smith, D., Lupoli, N., Mercado-García, A., Lamadrid-Figueroa, H., Tellez-Rojo, M. M., Hu, H., & Hernández-Avila, M. (2013). Maternal blood, plasma, and breast milk lead: lactational transfer and contribution to infant exposure. *Environmental Health Perspectives*, **122**, pp.87-92. Doi: https://doi.org/10.1289/ehp.1307187

Farzan, S. F., Brickley, E. B., Li, Z., Gilbert-Diamond, D., Gossai, A., Chen, Y., Howe, C. G., Palys, T. & Karagas, M. R. (2017). Maternal and infant inflammatory markers in relation to prenatal arsenic exposure in a U.S. pregnancy cohort. *Environmental research*, **156**, pp.426-433. Doi: https://doi.org/10.1016/j.envres.2017.03.056

Findlay, A. (2005). The perils of planting. *Georgia Strait*, pp: 38-39.
Food and Agriculture Organization of the United Nations (2009). FOASTAT-Fertilizer. Food and Agriculture Organization of the United Nations. [Available at: http://www.fao.org/faostat/en/#data/RF accessed on 26/02/2019]

Gross, M. J., Barry, D. A. J. & Rudolph, D. L. (1998) Contamination in Ontario Farmstead Domestic Wells And Its Association With Agriculture. 1. Results from Drinking Water Wells. *Journal of Contaminant Hydrology*, **32,** pp. 267-293.

Gu, B., Ju, X., Chang, J., Ge, Y. & Vitousek, P.M. (2015). Integrated reactive nitrogen budgets and future trends in China. *Proceedings of the National Academy of Sciences of the United States of America,* **112**, pp.8792–8797. Doi: https://doi.org/10.1073/pnas.1510211112

Harter, T. (2009). Agricultural impacts on groundwater nitrate. *Hydrology*, **8**, pp.22-23.

Huang, J., Xu, J., Liu, X., Liu, J. & Wang, L. (2011). Spatial Distribution Pattern Analysis of Groundwater Nitrate Nitrogen Pollution in Shandong Intensive Farming Regions of China Using Neural Network Method. *Mathematical and Computer Modelling*, **54**, pp.995-1004. doi: https://doi.org/10.1016/j.mcm.2010.11.027

Indredavik, M., Vik, T. & Heyerdahl, S. (2005). Psychiatric symptoms and disorders in adolescents with low birthweight. *Child: Care, Health and Development*, **31(1),** pp.121–125. doi: https://doi.org/10.1111/j.1365-2214.2005.00500_1.x

Jokinen, M. (2002). Measuring newborns-does size really matter? *RCM Midwives Journal,* **5(5).**

Kramer, M. S., Platt, R., Yang, H., McNamara, H. & Usher, R.H. (1999) Are all growth-restricted newborns created equal(ly)? *Pediatrics*, **103(3),** pp.599–602. doi: https://doi.org/10.1542/peds.103.3.599

Kristjanson, P., Waters-Bayer, A., Johnson, N., Tipilda, A., Njuki, J., Baltenweck, I. & MacMillan, S. (2010). Livestock and women's livelihoods: A review of the recent evidence (Discussion Paper No. 20). Nairobi: ILRI.

Lundberg, J.O., Gladwin, M.T., Ahluwalia, A., Benjamin, N., Bryan, N.S., Butler, A., Cabrales, P., Fago, A., Feelisch, M., Ford, P.C., Freeman, P.A., Frenneaux, M., Friedman, J., Kelm, M., Kevil, C.G., Kim-Shapiro, D.B., Kozlov, A.V., Lancaster, J.R., Lefer, D.J., McColl, K., McCurry, K., Patel, R.P., Petersson, J., Rassaf, T., Reutov, V.P., Richteraddo, G.B., Schechter, A., Shiva, S., Tsuchiya, K., van Faassen, E.E., Webb, A.J., Zuckerbraun, B.S., Zweier, J.L. & Weitzberg, E. (2009). Nitrate and nitrite in biology, nutrition and therapeutics. *Nature Chemical Biology*, **5**, pp.865-869
Martínez-Mesa, J., González-Chica, D. A., Bastos, J. L., Bonamigo, R. R., & Duquia, R. P. (2014). Sample size: how many participants do I need in my research?. *Anais brasileiros de dermatologia*, **89(4),** pp.609-15. Doi: https://doi.org/10.1590/abd1806-4841.20143705

McDonald, J.H. (2014). Handbook of Biological Statistics (3rd ed.). Sparky House Publishing, Baltimore, Maryland.

Mehar, M., Mittal, S., & Prasad, N. (2016). Farmers coping strategies for climate shock: Is it differentiated by gender? *Journal of Rural Studies*, **44**, pp.123–131. Doi: https://doi.org/10.1016/j.jrurstud.2016.01.001

Mensinga, T.T., Speijers, G.J.A. & Meulenbelt, J. (2003) Health implication of exposure to Environmental nitrogenous compounds. *Toxicological Reviews,* **22(1)**, pp. 41-51.

Mondal, D., Lopez-Espinosa, M.J., Armstrong, B., Stein, C.R. & Fletcher, T. (2012). Relationships of perfluorooctanoate and perfluorooctane sulfonate serum concentrations between mother-child pairs in a population with perfluorooctanoate exposure from drinking water. *Environmental Health Perspectives*, **120**, pp.752–757. Doi: https://doi.org/10.1289/ehp.1104538

O'Sullivan, M., Rao, A., Banerjee, R., Gulati, K., & Vinez, M. (2014). Levelling the field: Improving opportunities for women farmers in Africa. Washington, DC: World Bank Group.

Pretty, J., Toulmin, C., & Williams, S. (2011). Sustainable intensification in African agriculture. *International Journal of Agricultural Sustainability*, **9(1),** pp. 5–24. Doi: https://doi.org/10.3763/ijas.2010.0583

Prüss-Ustün, A., Vickers, C., Haefliger, P., & Bertollini, R. (2011). Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environmental health: a global access science source*, ***10*****(9).** Doi: https://doi.org/10.1186/1476-069X-10-9

Rivers, C. N., Barrett, M. H., Hiscock, K. M., Dennis, P.P., Feast, N.A. & Lerner, D.N. (1996) Use of Nitrogen Isotopes to Identify Nitrogen Contamination Of The Sherwood Sandstone Aquifer Beneath The City Of Nottingham, UK. *Hydrogeology Journal*, **4**, pp. 90-102.

Savci, S. (2012). Investigation of Effect of Chemical Fertilizers on Environment. *APCBEE Procedia*,**1**, pp. 287-292. Doi: https://doi.org/10.1016/j.apcbee.2012.03.047

Shober, A.L. (2015) Nitrogen cycling in agriculture. [Available at: http://extension.udel.edu/factsheets/nitrogen-cycling-in-agriculture/ accessed on 02/02/2019]

Sönmez, ø., Kaplan M. & Sönmez, S.(2007) An Investigation Of Seasonal Changes In Nitrate Contents Of Soils And Irrigation Waters In Greenhouses Located In Antalya-Demre Region. *Asian Journal Of Chemistry*, **19(7),** pp. 5639-5646.

Sutton M.A., Bleeker A., Howard C.M., Bekunda M., Grizzetti B., de Vries W., van Grinsven H.J.M., Abrol Y.P., Adhya T.K., Billen G., Davidson E.A, Datta A., Diaz R., Erisman J.W., Liu X.J., Oenema O., Palm C., Raghuram N., Reis S., Scholz R.W., Sims T., Westhoek H. & Zhang F.S., with contributions from Ayyappan S., Bouwman A.F., Bustamante M., Fowler D., Galloway J.N., Gavito M.E., Garnier J., Greenwood S., Hellums D.T., Holland M., Hoysall C., Jaramillo V.J., Klimont Z., Ometto J.P., Pathak H., Plocq Fichelet V., Powlson D., Ramakrishna K., Roy A., Sanders K., Sharma C., Singh B., Singh U., Yan X.Y. & Zhang Y. (2013) Our Nutrient World: The challenge to produce more food and energy with less pollution. Global Overview of Nutrient Management. Centre for Ecology and Hydrology, Edinburgh on behalf of the Global Partnership on Nutrient Management and the International Nitrogen Initiative. [Available at: http://nora.nerc.ac.uk/id/eprint/500700/1/N500700BK.pdf accessed on 20/02/2019]

Ward, M.H. (2009) Too Much of a Good Thing? Nitrate from Nitrogen Fertilizers and Cancer:President's Cancer Panel - October 21, 2008. *Reviews on Environmental Health*, **24(4),** pp.357-363

World Health Organization (n.d.) Health Topics: Epidemiology. [Available at: https://www.who.int/topics/epidemiology/en/ accessed on 05/03/2019]

Wu, Y., Xi, X., Tang, X., Luo, D., Gu, B., Lam, S. K., Vitousek, P. M. & Chen, D. (2018). Policy distortions, farm size, and the overuse of agricultural chemicals in China. *Proceedings of the National Academy of Sciences of the United States of America*, **115(27),** pp.7010-7015.

Zhang, X.N., Guo, Q.P., Shen, Q.P., Yu, S.W. & Qui, G.Y. (2015). Food Safety Special Issue: Water quality, agriculture and food safety in China: current situation, trends, interdependencies, management. *Journal of Integrative Agriculture.*