**Question: Is occupational nitrous oxide exposure associated with adverse impacts on fertility or pregnancy outcomes?**

Literature review conducted 05/04/2023 (search terms: nitrous oxide, occupational, pregnancy)

Also reviewed literature quoted in Reprotox and TERIS.

*Evidence quality and limitations impacting interpretation*

Clinical data regarding occupational exposure to nitrous oxide is considered to be of poor quality with studies utilising retrospective questionnaire-based evidence that was generally collected in the 1980-90s. It is therefore possible that these data may not reliably predict risks in modern settings, and given the methods used to collect these data, the studies are considered limited by retrospective reporting bias and sampling bias. Generally, the studies also lacked adequate control groups and are the findings are therefore likely impacted by uncontrolled confounders (e.g. shift work, physical strain, and possible exposure to other toxicants). Finally, no studies have been located regarding known exposure to nitrous oxide exceeding permitted occupational levels.

*Miscarriage*

Quick summary: The available data regarding occupational exposure to nitrous oxide and miscarriage (variably defined as a fetal loss prior 20-24 weeks gestational age) are contradictory and confounded. The evidence does not provide conclusive proof of an association between occupational nitrous oxide exposure and miscarriage.

Studies in female dental personnel have shown a relative risk of miscarriage of 2.6 (95% CI 1.3 to 5.0) associated with exposure to un-scavenged nitrous oxide.[1-3] In contrast, the frequency of miscarriage was no greater than expected among 352 pregnancies in dental assistants with occupational exposure to nitrous oxide in a study from Denmark (OR 1.0; 95% CI 0.8 to 1.2).[4]

In a questionnaire study of Swedish midwives, occupational exposure to nitrous oxide in pregnancy was not associated with an increased risk of miscarriage (OR 0.95; 95% CI 0.62 to 1.47),[5]

A study of Dutch nurses included those allocated to tonsil removal surgery and those assisting in operating rooms (and hence likely exposed to NO alongside other occupational exposures). There was an approximate 2-fold increased risk of miscarriage described for both groups (aOR 1.9, 95% CI 1.1 to 3.6 and aOR 1.8, 95% CI 1.0 to 4.1 respectively).[7] While the risk estimates did adjust for covariates, such as working under time pressure, working night shift, heavy lifting, chemical use for sterilising/disinfection, and exposure to cytostatic drugs and antibiotics, given that the finding was observed in both groups, it is possible that nitrous oxide exposure may not be the causative factor for the increased risks described. Unfortunately, this study was published in Dutch, and I have not been able to assess the crude data to see if the nurses were exposed whilst pregnant or before pregnancy.

*Congenital malformation*

Quick summary: There are few studies investigating malformation risk following occupational exposure to nitrous oxide. The available data are also conflicting and highly confounded. Although associations with malformation have been described, due to the data limitations, the evidence does not provide conclusive proof of an association between occupational nitrous oxide exposure and congenital malformation.

An association with probable occupational exposure to nitrous oxide during the first trimester of pregnancy was observed in 1,079 infants with congenital anomalies born to registered nurses in Canada (OR 1.82; 95% CI 1.11 to 2.99).[8] Of five anatomic classes of congenital anomalies examined in this study, the association was strongest for abnormalities of the skin. This finding was produced from a case-control study, which undertook multiple comparisons but did not undertake an analysis to account for chance findings due to statistical error. The study also only adjusted the findings for covariable risk factors for malformation including the pregnancy year and mother’s age. Associations were also observed for exposure to halogenated anaesthetic gases. No association with occupational nitrous oxide exposure during the first trimester of pregnancy was seen among 31 women veterinarians who had children with congenital anomalies.[9]

In the study of Dutch nurses described above (see miscarriage section), an approximate 2-fold increased risk of congenital malformation was observed among the infants of nurses who assisted in the operating room.[7] The same limitations as described above also apply here.

*Fetal growth and preterm delivery*

Quick summary: A single study has suggested that occupational exposure to nitrous oxide could increase the risk of small for gestational age. As there are no additional studies to confirm or refute this finding, and the study may be confounded and/or influenced by methodological biases, this study alone does not provide sufficient evidence of a risk.

In a questionnaire study of Swedish midwives, occupational exposure to nitrous oxide in pregnancy was associated with a 3-fold increase in small for gestational age (OR 3.0; 95% CI 1.2 to 7.2 – adjusted to consider differences in parity, maternal age, extent of employment and shift work patterns between those exposed and unexposed to nitrous oxide), but not preterm delivery.[6] I have not located any additional information

*Fertility*

Quick summary: A possible association with impaired fertility has been described in one study. As there are no additional studies to confirm or refute this finding and as the study findings may be confounded (despite the robust methods of both data collection and analysis), this study alone does not prove that occupational exposure to nitrous oxide poses a risk to female fertility.

In a questionnaire study attempting to address concerns about female fertility, data were sought from 7,000 dental assistants and included an estimation of their exposure to nitrous oxide as well as their time to conception.[10] However, analysis was possible on only 459 replies because of exclusion through insufficient data or predefined criteria. From this limited data set, the authors concluded that un-scavenged nitrous oxide exposure (which they estimated to exceed 1,000 ppm) was associated with a slight reduced ability to conceive (fecundability ratio – 0.94, 95% CI; 0.90 to 0.98). When the analysis was stratified by amount of occupational exposure time, exposure to ≥5 hours per week produced a more significant decrease in fecundability ratio (0.41 , 95% CI; 0.23 to 0.74). This highest level of exposure also showed a notable increase in the mean number of cycles to conception compared with other groups, and a decrease in the proportion who became pregnant within the first cycle.

This study utilised a robust methodological approach to both data collection and analysis, restricting the dataset to those with complete data and analysing a large number of co-variable risk factors and occupational exposures. However, as with all observational studies, the findings may still be confounded, which mean the study cannot be considered conclusive regarding the risk to female fertility. However, some of the findings above are notable (higher levels of exposure correlating with considerably longer time to pregnancy), meaning that the findings cannot be discounted.

*Conclusion*

This is not an exhaustive review of the published literature. Although some but not all studies have reported increased risks of miscarriage, congenital malformation, small for gestational age, and adverse effects on female fertility following occupational exposure to nitrous oxide, much of the evidence is limited and subject to numerous sources of bias and confounding. As a consequence, we do not currently consider the available data demonstrates sufficient evidence that occupational exposure to nitrous oxide poses a major risk to the developing fetus. However, it is important to note that these studies have not investigated the risk of exposure to nitrous oxide exceeding permitted occupational levels. As such, it is not possible to conclude that exposure to high occupational levels of nitrous oxide does not pose a risk to the fetus. A single study has provided a possible indication of an association with impaired fertility, particularly with exposure to higher doses where nitrous oxide is un-scavenged. However, it is difficult to know how well the findings from this observational study relate to the occupational exposures which have occurred in your hospital.

*References*

1. Rowland AS, Baird DD, Shore DL, Weinberg CR, Savitz DA, Wilcox AJ. Nitrous Oxide and Miscarriage in Female Dental Assistants. American Journal of Epidemiology. 1995;141(6):531-8.

2. Gray RH. Nitrous oxide and fertility. (0028-4793 (Print)).

3. Rowland A, Baird D, Weinberg C. Nitrous oxide and fertility. (reply). N Engl J Med. 1993;328:284.

4. Heidam LZ. Miscarriages among dental assistants, factory workers, painters, and gardening workers: a follow up study. Journal of Epidemiology and Community Health. 1984;38(2):149.

5. Axelsson G, Ahlborg G, Bodin L. Shift work, nitrous oxide exposure, and miscarriage among Swedish midwives. Occupational and Environmental Medicine. 1996;53(6):374.

6. Bodin L, Axelsson G, Ahlborg G, Jr. The Association of Shift Work and Nitrous Oxide Exposure in Pregnancy with Birth Weight and Gestational Age. Epidemiology. 1999;10(4).

7. Peelen S, Roeleveld N, Heederik D, Kromhout H, de Kort W. Reproductie-toxische effecten bij ziekenhuispersoneel. 1999.

8. Teschke K, Abanto Z, Arbour L, Beking K, Chow Y, Gallagher RP, et al. Exposure to anesthetic gases and congenital anomalies in offspring of female registered nurses. American Journal of Industrial Medicine. 2011;54(2):118-27.

9. Johnson JA, Buchan RM, Reif JS. Effect of Waste Anesthetic Gas and Vapor Exposure on Reproductive Outcome in Veterinary Personnel. American Industrial Hygiene Association Journal. 1987;48(1):62-6.

10. Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced Fertility among Women Employed as Dental Assistants Exposed to High Levels of Nitrous Oxide. New England Journal of Medicine. 1992;327(14):993-7.