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Health Effects Associated With Exposure to Anesthetic Gas Nitrous Oxide-N_2O in Clinical Hospital – Shtip Personel

Bilijana Eftimova[1*], Marija Sholjakova[2], Dejan Mirakovski[3], Marija Hadzi-Nikolova[3]

[1]Department of Anesthesia and Intensive Care, Clinical Hospital, Shtip, Republic of Macedonia; [2]Department of Anesthesia, Medical Faculty, Ss. Cyril and Methodius University of Skopje, Skopje, Republic of Macedonia; [3]Univeristy "Goce Delcev", Faculty of Natural and Techncial Scinces, AMBICON Lab, Shtip, Republic of Macedonia

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***Correspondence:** Bilijana Eftimova. Department of Anesthesia and Intensive Care, Clinical Hospital, Shtip, Macedonia. E-mail: beftimova@yahoo.com

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Abstract

AIM: To show certain health effects associated with acute and chronic exposure to nitrous oxide of staff of the Department of Anaesthesiology and Intensive Care at the Clinical Hospital in Shtip.

METHODS: A transversal study was conducted, that include 43 health workers (23 – exposed and 20 - unexposed). Personal exposure to nitrous oxide for this group members was assessed through continuous measurement over 8 hours shift within breathing zone of the subjects involved, using handheld electrochemical instrument with datalogging option direct. In order to determine presence of possible health effects associated with acute and chronic exposure to nitrous oxide in ORs and ICUs, a specially designed questionnaire was prepared and distributed to be anonymously filled out, by all the examinees from both examined groups. Data were statistically tested for normality and also quantitative and qualitative assessment was performed.

RESULTS: From the results obtained, a significant difference in several health effects between exposed and unexposed groups can be noted, including headaches, dizziness, nausea and vomiting, euphoria and tachycardia. Regarding the excitement, the appearance of depression, the feeling of numbness and tingling of the hands and feet, the differences between the two examined groups were not significant.

CONCLUSION: It can be concluded that chronic exposure to nitrous oxide is associated with the adverse health effects.

Introduction

Nitrous oxide, also known as "Laughing Gas", is anaesthetic gas still extensively used in general anaesthesia in Operating Rooms (ORs) in many hospitals worldwide. Staff administering this anaesthetic gas to patients is also exposed to its influence, which is particularly pronounced in long-term chronic exposure, situation commonly occurring in the technically underequipped hospitals [1-4]. In doing so, its harmful effects on the health of the medical staff become more pronounced and are associated with acute and chronic exposure to nitrous oxide.

The health effects of acute exposure include occurrence of headache, dizziness, nausea/vomiting, depression, reduced number of white and red blood cells, anxiety, tremor, decreased motor and audio-visual skills, excitation, euphoria and elevated intracranial pressure due to hypoxia. Acute exposures to nitrous oxide cause acute disorders, which adequately treated can be cured in short period. Long-term chronic exposure usually associated with professional exposures in ORs and ICUs, induce more expressed health effects and large damage, that is directly correlated with the period and intensity of exposure. These include the toxic effect of the peripheral nervous system, that lead to neurological symptoms beginning with tingling or numbness of the arms or legs, that later arise becoming similar like those of subacute combined degeneration of the spinal cord. All symptoms are improved by stopping the exposure [5-12].

It is also possible that the nitrous oxide can cause disorder by including in the action of vitamin B12 on the nervous system. As proven, the nitrous oxide can cause irreversible deactivation of vitamin B12 - dependent methionine synthase [13-15]. Disturbances in cell proliferation with megaloblastic anaemia are generally quite small. However, continuous administration after 24 hours or repeated administration more often than once every 3 to 4 days will result in leucopenia and megaloblastic changes. In the case of shorter exposure, there is a predominance of alpha-adrenergic stimulation (increased peripheral vascular resistance and blood pressure increase). On the other hand, exposure to higher concentrations over a longer period can induce predominance of beta-adrenergic activation with increased cardiac output, increased heart rate, increased blood pressure, increased muscle blood flow, and decreased systemic vascular resistance. Exposure to nitrous oxide causes a moderate increase in the tone of the sympathetic system with subsequent moderate vasoconstriction of the splanchnic vascular system leading to a reduction in v. portae blood flow and moderate vasoconstriction of the hepatic arterial system. As mentioned above, nitrous oxide is known as an inhibitor of the enzyme methionine synthetase in the liver, so long-term exposure can lead to toxic hepatic effects [16-19].

Nitrous oxide can also cause depression of leukocyte production, their motility, and leukocytes chemotaxis, which indirectly affects cellular immunity. Immunological disorders due to chronic exposure have been documented [13, 15, 20].

Some studies also report nitrous oxide effects of teratogenicity or increase of spontaneous abortion incidence among women exposed. It is also considered, that there is an increased incidence of congenital anomalies in offspring of women professionally exposed during pregnancy and spontaneous abortion in women of professionally exposed men's [21, 22].

Purpose of this paper is to show certain health effects associated with acute and chronic exposure to nitrous oxide-N2O in the ORs to the staff of the Department of Anaesthesiology and Intensive Care (DAIC) at the Clinical Hospital (CH) - Shtip.

Material and Methods

The paper presents a transversal study, conducted in the period from 01.12. until 31.12.2014, at the CH - Shtip, Macedonia. A total of 43 health workers have been investigated, of which 23 staff members from the DIAC that are exposed to nitrous oxide in operating rooms and intensive care units (exposed group - N1), and 20 staff members from the Department of Internal Medicine (unexposed or control group - N2). Exposed group includes MD anaesthesiologists, nurses' anaesthetists and paramedics. Personal exposure to nitrous oxide for this group members was assessed through continuous measurement over 8 hours shift within breathing zone of the subjects involved, using handheld electrochemical instrument with datalogging option direct. During the study, all staff members from exposed group wear the instrument, thus allowing for continuous 8 hours monitoring in their real microenvironment.

In order to determine presence of possible health effects associated with acute and chronic exposure to nitrous oxide in ORs and ICUs, a specially designed questionnaire was prepared and distributed to be anonymously filled out, by all the examinees from both examined groups.

The distribution of quantitative data from the research was tested with the Test for normality: Kolmogorov-Smirnov test and Shapiro-Wilk W test. The description of the quantitative data was made with the measures of the central tendency (arithmetic means and averages) and the measures of dispersion (standard deviations). Qualitative assessment was performed with relations and proportions; testing the significance of differences between two proportions in independent samples (exposed / non-exposed) was done with the nonparametric Mann-Whitney U Test; testing the significance of the differences between two arithmetic means under normal distribution was done with a Student - t test for independent samples; and risk of occurrence of certain health effects associated with acute and chronic exposure to nitrous oxide was calculated by Odds ratio (OR) and Relative Risk (RR); All results where the value of $p < 0.05$ with interval of confidence CI = 95%, were considered to be significant.

The survey included a total of 43 health workers, divided into two groups according to their current and past exposure to nitrous oxide during routine work in CH - Shtip. The investigated group (N1-exposed) include 23 staff members of which 8 (34.8%) MD anaesthesiologists, 13 (56.5%) anaesthetic nurses and 2 (8.7%) paramedics, all from the DAIC, who were exposed to nitrous oxide in ORs and ICUs. Control group (N2 - unexposed) include 20 staff members of which 7 (35%) MD, 11 (55%) nurses, and 2 (10%) paramedics working in the Department of Internal Medicine (DIM) at the CH - Shtip.

Investigated groups were found to be homogeneous in terms of gender, age and length of work experience. In terms of sex, there was no significant difference between the respondents of the two examined groups (Mann-Whitney U Test: $Z = 0.389$ $p = 0.6968$). In terms of age (Student t-test: $t = -0.2046$, $p = 0.8389$), as well as in terms of work experience of exposed and unexposed health workers (Student t-test: $t = -0.233$ $p = 0.8164$), the differences

were also not significant. The average length of work experience in the operating room of the respondents from the DIAC was 15.62 ± 12.31 years (min = 1 year, max = 40 years), and the average number of hours spent in the operating room during one working day is 5.44 ± 1.52 (min = 1 hour; max = 7 hours).

Table 1: Distribution of respondents by gender, age, working experience, working experience in the operating room and number of hours per day in the operating room

Parameter / variable	N1 - exposed	N2- unexposed
Sex	Women - 20 (87%) Man – 3 (13%)	Women - 16 (80%) Man – 4 (20%)
Age	45.68 ± 10.67	45.10 ± 7.98
Work experience (years)	18.95 ± 12.82	18.16 ± 8.65
Ors work experience (years)	15.62 ± 12.31	/
Working hours in ors	5.44 ± 1.52	/

Table 2 gives the distribution of respondents from both examined groups, as well as the significance of differences in relation to the specific health effects. Staff members from the DAIC (N1 - exposed), in relation to the healthcare workers from the DIM (N2-unexposed) at the CH - Shtip, statistically have significantly more often headaches (p = 0.0040), dizziness (p = 0.0068), nausea and vomiting (p = 0.0408), euphoria (p = 0.0028) and tachycardia (p = 0.023), (Table 2 and Figure 1). Regarding the excitement, the appearance of depression, the feeling of numbness and tingling of the hands and feet, the differences between the two examined groups were not significant. The systolic blood pressure of the exposed staff members was on average 120.7 ± 22.6 (min = 90; max = 160), and for the unexposed on average 124.7 ± 24.5 (min = 100; max = 200), the differences were found not to be significant (Mann-Whitney U Test: Z = 0.325 p = 0.7451). The diastolic blood pressure of the exposed health workers was on average 75.5 ± 10.94 (min = 60; max = 90), and for unexposed 79.2 ± 10.31 (min = 60; max = 100), so the differences were also not significant (Mann-Whitney U Test: Z = 0.853 p = 0.3935).

Table 2: Distribution of examinees from both examined groups and significance of difference in relation to certain health effects

Health effects	N1 – exposed (n = 23)		N2 - unexposed (n = 20)		Significance P
	Yes	No	Yes	No	
Headache	2 (8.7%)	21 (91.3%)	12 (60%)	8 (40%)	P = 0.0040*
Dizziness	5 (21.7%)	18 (78.3%)	14 (70%)	6 (30%)	P = 0.0068*
Nausea / vomiting	10 (43.5%)	13 (56.5%)	16 (80%)	4 (20%)	P = 0.0408*
Euphoria	5 (21.7%)	18 (78.3%)	15 (75%)	5 (25%)	P = 0.0028*
Excitement	7 (30.4%)	16 (69.6%)	11 (55%)	9 (45%)	P = 0.0703
Depression	17 (73.9%)	6 (26.1%)	17 (85%)	3 (15%)	P = 0.5346
Stiffness of the hands / feet	14 (60.9%)	9 (39.1%)	16 (80%)	4 (20%)	P = 0.2840
Tingling of hands / legs	12 (52.2%)	11 (47.8%)	15 (75%)	5 (25%)	P = 0.2011
Hypertension	17 (73.9%)	6 (26.1%)	12 (60%)	8 (40%)	P = 0.4358
Tachycardia	6 (26.1%)	17 (73.9%)	13 (65%)	7 (35%)	P = 0.0293*
Women-spontaneous abortion	14 (70%)	6 (30%)	13 (81.3%)	3 (18.7%)	P = 0.5666
Mens azoo / oligospermia	3 (100%)	/	4 (100%)	/	P = 1.0
Renal calculus	23 (100%)	/	20 (100%)	/	P = 1.0

Spontaneous abortion confirmed among women in exposed group was 6 (30%) and among women in unexposed group 3 (18.7%), with the difference assessed as statistically not significant (p = 0.5666). The occurrence of renal calculus in the examinees from both examined groups as well as azoo/oligospermia in male examinees was not noted.

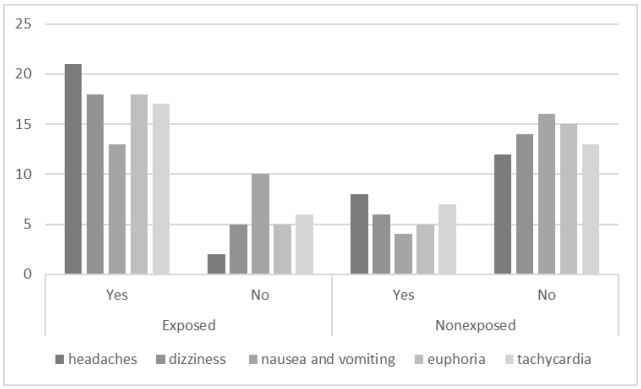

Figure 1: Distribution of the respondents from the two examined groups according to the presence of frequent headaches, dizziness, nausea and vomiting, euphoria and tachycardia

The risk of the occurrence of certain health effects associated with acute and chronic exposure to the nitrous oxide was calculated using the Odds ratio (OR) and Relative Risk (RR).

The analysis showed that exposure to nitrous oxide is a risk factor for frequent headache in health care workers (OR = 15.75; 95% confidence interval; 2.86 to 86.57). The relative risk is 5.06 and shows that for the exposed workers, risk of occurrence of frequent headaches is 5 times higher than in the unexposed persons (Table 3).

Table 3: Risk of occurrence of certain health effects due to exposure to nitrous oxide

Health effects	Odds ratio (OR)	Relative Risk (RR)
Headache	OR = 15.75 95% CI; 2.86 to 86.57	RR = 5.06 95% CI; 1.37 to 18.64
Dizziness	OR = 8.40 95% CI; 2.11 to 33.29	RR = 2.85 95% CI; 1.29 to 6.26
Nausea / vomiting	OR = 5.20 95% CI; 1.31 to 20.48	RR = 1.89 95% CI; 1.14 to 3.45
Euphoria	OR = 10.80 95% CI; 2.61 to 44.52	RR = 3.13 95% CI; 1.42 to 6.89
Excitement	OR = 2.79 95% CI; 0.79 to 9.76	RR = 1.64 95% CI; 0.85 to 3.15
Depression	OR = 2.0 95% CI; 0.42 to 9.33	RR = 1.33 95% CI; 0.75 to 2.36
Stiffness of the hands / feet	OR = 2.57 95% CI; 0.64 to 10.21	RR = 1.48 95% CI; 0.87 to 2.51
Tingling of hands / legs	OR = 2.75 95% CI; 0.74 to 10.10	RR = 1.54 95% CI; 0.90 to 2.64
Hypertension	OR = 0.52 95% CI; 0.14 to 1.92	RR = 0.73 95% CI; 0.37 to 1.43
Tachycardia	OR = 5.26 95% CI; 1.42 to 19.46	RR = 2.24 95% CI; 1.10 to 4.56
Women-spontaneous abortion	OR = 1.85 95% CI; 0.38 to 9.0	RR = 1.28 95% CI; 0.71 to 2.31

Nitrous oxide exposure is also a risk factor for the occurrence of dizziness in our exposed subjects (OR = 8.40; 95% confidence interval; 2.11 to 33.29). The risk of dizziness in exposed subjects is 2.85 times greater than that of the unexposed (Table 3).

Acute and chronic exposure to anaesthetic gas N_2O is a significant risk factor for the occurrence of nausea and vomiting (OR = 5.20; 95% CI; 1.31 to

20.48), euphoria (OR = 10.80 95% CI; 0.61 to 44.52) and an occurrence of tachycardia (OR = 5.26 95% CI; 1.42 to 19.46). The risk of nausea and vomiting is 1.98 times higher in those exposed than in the unexposed. The risk of euphoria is 3.13 and for tachycardia 2.24 times higher for those exposed to anaesthetic gas compared to the unexposed respondents (Table 3).

Regarding the other examined parameters, the analysis showed that anaesthetic gas is not a significant risk factor.

Discussion

From the results obtained, a significant difference in several health effects between exposed and unexposed groups can be noted. The survey has included homogeneous groups in terms of gender, age and length of work experience. This was done to avoid the impact of these parameters to the results or changes in certain health parameters between exposed and unexposed staff members. Regarding the health effects studied, statistically significant differences were obtained for certain parameters including, the headache in the exposed compared to the unexposed statistically is significantly higher (n = 0.0040), dizziness also (n = 0.0068), and same goes to nausea / vomiting (n = 0.0408), euphoria (n = 0.0028), and tachycardia (n = 0.0293). These conclusions were reported in the very beginnings of the use of nitrous oxide for medical purposes by [2, 5-7, 21, 23, 24].

Investigations for the toxic effects of nitrous oxide continued more recent dates, so his neurotoxicity with increasing of intracranial pressure and subsequent headaches, dizziness, nausea and vomiting continued to be proven and pointed as symptoms in cases of chronic exposures [21, 23-25].

On the other hand, symptoms such as excitement and euphoria (n = 0.0703), depression (n = 0.5436), numbness of the limbs (n = 0.2846), tingling of the hands (n = 0.2011), increased blood pressure n = 0.4358), renal calculus (n = 1) did not show statistically significant differences. However, such effects were observed in respondents and reported elsewhere and therefore they should not be neglected.

Regarding spontaneous abortions among female staff as well as azoospermia in men, the statistic difference was not significant either because of the age of the respondents, or the that most of the male respondents refused to discuss these issues, although large number of studies reported relations between fertility and nitrous oxide [25, 26].

According to the results obtained, it can be concluded that chronic exposure to nitrous oxide is associated with the adverse health effects. Major complaints in exposed group are headache, dizziness, nausea, vomiting, euphoria, and tachycardia. Those effects show statistically significant differences compared to unexposed group. On the other side, it has been proven that safe exposure levels are feasible and can be achieved if proper control techniques are in place and properly used. Therefore, proper work (worktime reduction, rotation, proper staffing) practices and application of control equipment (general ventilation and scavenging systems) in ORs is of upmost importance for reduction of chronic exposure and associated health effects.

References

1. Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. Anesth Prog. 2007; 54 (1):9-18. https://doi.org/10.2344/0003-3006(2007)54[9:AIUTAO]2.0.CO;2

2. Sadigh Maroufi Sh, Gharavi MJ, Behnam M, Samadikuchaksaraei A. Nitrous Oxide Levels in Operating and Recovery Rooms of Iranian Hospitals. Iranian Journal of Public Health. 2011; 40(2): 75-79. PMid:23113075 PMCid:PMC3481765

3. Parlow JL, Milne B, Tod DA, Stewart GI, Griffiths JM, Dudgeon DJ. Self-administered nitrous oxide for the management of incident pain in terminally ill patients: a blinded case series. Palliat Med. 2005; 19(1):3-8. https://doi.org/10.1191/0269216305pm958oa PMid:15690862

4. Baum VC, Willschke H, Marciniak B. Is nitrous oxide necessary in the future? Paediatric Anaesthesia. 2012: 22(10): 981–7. https://doi.org/10.1111/pan.12006 PMid:22967156

5. Krajewski W, Kucharska M, Wesolowski W, Stetkiewicz J, Wronska-Nofer T. Occupational exposure to nitrous oxide – the role of scavenging and ventilation systems in reducing the exposure level in operating rooms. International Journal of Hygiene and Environmental Health. 2007; 210:133-38. https://doi.org/10.1016/j.ijheh.2006.07.004 PMid:17045524

6. Wiesner G, Hoerauf K, Schroegendorfer K, et al. High-level, but not low-level, occupational exposure to inhaled anaesthetics is associated with genotoxicity in the micronucleus assay. Anaesthesia & Analgesia. 2001; 92: 118–22. https://doi.org/10.1097/00000539-200101000-00023

7. Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW. A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Research. 2001; 895: 264–267. https://doi.org/10.1016/S0006-8993(01)02079-0

8. Fujinaga M, Maze M. Neurobiology of nitrous oxide-induced antinociceptive effects. Mol Neurobiol. 2002; 25(2): 167–89. https://doi.org/10.1385/MN:25:2:167

9. Jevtovic-Todorovic V, Beals J, Benshoff N, Olney JW. Prolonged exposure to inhalational anaesthetic nitrous oxide kills neurons in adult rat brain. Neuroscience. 2003; 122: 609–616. https://doi.org/10.1016/j.neuroscience.2003.07.012 PMid:14622904

10. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anaesthesiology. 2008; 109(4): 707-722. https://doi.org/10.1097/ALN.0b013e3181870a17 PMid:18813051

11. Branpton P. Review of Toxicological Data on Nitrous Oxide. Brussels: European Industrial Gases Association (EIGA), 2008.

12. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anaesthesiology. 2008;109:707–22. https://doi.org/10.1097/ALN.0b013e3181870a17 PMid:18813051

13. Krajewski W, Kucharska M, Pilacik B, Fobker M, Stetkiewicz J, Nofer JR, et al. Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. British Journal of Anaesthesiology. 2007; 99: 812–18. https://doi.org/10.1093/bja/aem280 PMid:17951609

14. Scapellato ML, Mastrangelo G, Fedeli U, Carrieri M, Macca I, Scoizzato L, et al. A longitudinal study for investigating the exposure level of anaesthetics that impairs neurobehavioral performance. Neurotoxicology. 2008; 29:116–23. https://doi.org/10.1016/j.neuro.2007.10.001 PMid:18022695

15. Sardas S, Izdes S, Ozcagli E, Kanbak O, Kadioglu E. The role of antioxidant supplementation in occupational exposure to waste anaesthetic gases. International Archives of Occupational and Environmental Health. 2006; 80:154–159. https://doi.org/10.1007/s00420-006-0115-6 PMid:16710711

16. Pichardo D, Luginbuehl IA, Shakur Y, Wales PW, El-Sohemy A, O'Connor DL. Effect of nitrous oxide exposure during surgery on the homocysteine concentrations of children. Anaesthesiology. 2012; 117(1): 15-21. https://doi.org/10.1097/ALN.0b013e318259a8cc PMid:22584536

17. lee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clinical Chemistry. 2000; 46:1277-83. PMid:10926922

18. Guttormsen AB, Refsum H, Ueland PM. The interaction between nitrous oxide and cobalamin Biochemical effects and clinical consequences. Acta Anaestesiologica Scandinavica. 1994; 44: 653-7.

19. Badner NH, Beattie S, Freeman D, Spence JD. Nitrous oxide-induced elevated homocysteine concentrations are associated with increased myocardial ischemia in patients undergoing carotid endartectomy. Anesthesia & Analgesia. 2001; 91:1073-9.

20. Foschi D, Rizzi A, Zighetti ML, et al. Effects of surgical stress and nitrous oxide anaesthesia on peri-operative plasma levels of total homocysteine. Anaesthesia. 2001; 56: 676-7. https://doi.org/10.1046/j.1365-2044.2001.01374-2.x PMid:11437770

21. Fujinaga M, Baden JM, Yhap EO, Mazze RI. Reproductive and teratogenic effects of nitrous oxide, isoflurane, and their combination in Sprague-Dawley rats. Anaesthesiology. 1987; 67(6): 960–964. https://doi.org/10.1097/00000542-198712000-00014

22. Olfert SM. Reproductive outcomes among dental personnel: a review of selected exposures. J Can Dent Assoc. 2006; 72: 821–25. PMid:17109802

23. Jevtovic-Todorovic V, Benshoff N, Olney JW. Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. British Journal of Pharmacology. 2000; 130: 1692–1698. https://doi.org/10.1038/sj.bjp.0703479 PMid:10928976 PMCid:PMC1572233

24. Jevtovic-Todorovic V, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998; 4(4): 460–3. https://doi.org/10.1038/nm0498-460 PMid:9546794

25. Health Council of the Netherlands: Committee for Compounds toxic to reproduction. Nitrous oxide; Evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands, publication no. 2000/03 OSH, 2000.

26. Judith P, Rooks. Safety and Risks of Nitrous Oxide Labor Analgesia: A Review. Journal of Midwifery &Women's Health. 2011; 56(6): 557-65. https://doi.org/10.1111/j.1542-2011.2011.00122.x PMid:22060215