Gestational Exposure to High Perchlorate Concentrations in Drinking Water and Neonatal Thyroxine Levels

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Objective: To assess the effect of gestational perchlorate exposure through drinking water on neonatal thyroxine (T4).

Design: T4 values were compared among newborns in Ramat Hasharon, Israel, whose mothers resided in suburbs where drinking water contained perchlorate ≥340 μg/L (very high exposure, n = 97), 42–94 μg/L (high exposure, n = 216), and <3 μg/L (low exposure, n = 843). In the very high and high exposure areas, T4 values in newborns whose mothers drank tap water exclusively (as determined by a telephone interview) were analyzed as a subset. Serum perchlorate levels in blood from donors residing in the area were used as proxy indicators of exposure.

Main outcome: Neonatal T4 values (mean ± SD) in the very high, high, and low exposure groups were 13.9 ± 3.8, 13.9 ± 3.4, and 14.0 ± 3.5 μg/dL, respectively (p = NS). Serum perchlorate concentrations in blood from donors residing in areas corresponding to these groups were 5.99 ± 3.89, 1.19 ± 1.37, and 0.44 ± 0.55 μg/L, respectively. T4 levels of neonates with putative gestational exposure to perchlorate in drinking water were not statistically different from controls.

Conclusion: This study finds no change in neonatal T4 levels despite maternal consumption of drinking water that contains perchlorate at levels in excess of the Environmental Protection Agency (EPA) drinking water equivalent level (24.5 μg/L) based on the National Research Council reference dose (RfD) [0.7 μg/(kg · day)]. Therefore the perchlorate RfD is likely to be protective of thyroid function in neonates of mothers with adequate iodide intake.

Introduction

Perchlorate can affect thyroid function by competitive inhibition of iodide uptake into the thyroid. Potassium perchlorate was used in the 1950s and 1960s for treatment of hyperthyroidism at doses of 400–2000 mg/day for many weeks or months. This use of perchlorate ceased by the late 1960s because it was found to cause aplastic anemia and agranulocytosis, including seven fatalities (1,2). Interest in perchlorate has resurfaced due to its widespread contamination of drinking water from military and other industrial uses. In Arizona, California, and Nevada alone, the drinking water supply for about 20 million people is contaminated to some degree by perchlorate (3). The range of proposed regulation of perchlorate in drinking water varied between 2 μg/L (4) and 220 μg/L, as suggested by the Department of Defense (5). A too stringent drinking water standard for perchlorate would necessitate an expensive clean-up as 35 states have more than 4 μg/L of perchlorate in drinking water. Drinking water standards are preferably based on risk assessment of the critical effect of a chemical in humans when data are available (6). To account for the intraspecies variability, studies should consider the most sensitive population—in the case of perchlorate, fetuses of pregnant women (2). The National Research Council (NRC) of the National Academy of Sciences recommended a reference dose (RfD) of 0.7 μg/(kg · day) based on a clinical study of 37 adult volunteers by Greer et al. (1). In this study, the no-observed-effect level (NOEL) for inhibition of iodide uptake by the thyroid was 7 μg/(kg · day) perchlorate. An additional uncertainty factor of 10 was introduced to protect the most sensitive population, that is, fetuses of pregnant women. A drinking water equivalent level (DWEL) of 24.5 μg/L can be extrapolated from the RfD based on a 70-kg person drinking 2 L water/day, and no perchlorate exposure from other sources.

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Data on the effect of perchlorate exposure on thyroid function in susceptible populations would provide a stronger basis for risk assessment. Several epidemiological studies have assessed the association between exposure to perchlorate in pregnant women and thyroid function of their offspring (3,7–11). Perchlorate concentrations in drinking water were up to 115–120 μg/L in two studies from Chile (8,12), and <16 μg/L in five reports from the United States. All studies except that of Brechner et al. (3) showed no association between exposure to perchlorate in pregnant women and effect on thyroid functions in their newborns. The methodology of the Brechner study has been severely criticized (13,14). These U.S. studies, as well as the present study (see “Discussion”), were conducted in iodine-sufficient areas and did not include individual iodine status measures. These studies are insufficient because, with the exception of Tellez et al. (12), they were ecological studies, which did not ascertain actual exposure of the individual pregnant mother to perchlorate. The Tellez et al. (12) study from Chile reported direct measurements of perchlorate intake and showed that gestational exposure to perchlorate at 114 μg/L in drinking water did not cause changes in neonatal thyroid function or fetal growth retardation. This study had not been peer reviewed at the time of the NRC assessment. Direct evidence on the effect of gestational perchlorate exposure on thyroid functions of newborns in humans was judged inadequate; therefore, experimental data in adults were reviewed as a second best alternative. Since the critical effect of perchlorate is impaired thyroid function in human fetuses, data on the effect of high gestational exposure to perchlorate on the thyroid function of newborns would contribute to a more reliable basis for its regulation in drinking water.

Herein we tested the null hypothesis that there would be no significant differences in neonatal thyroxine (T4) levels following high gestational exposure to perchlorate in drinking water, in iodine-sufficient pregnant women. Our study addressed perchlorate concentrations in drinking water that were substantially above the recommended DWEL of the EPA as derived from the RfD established by the NRC (2).

Materials and Methods

Population and water perchlorate data

Ramat Hasharon is a city located in central Israel close to the Mediterranean coast with 35,600 inhabitants in 2004. Perchlorate contamination of groundwater was found in local wells that had been in the vicinity of a military plant that was active for decades (Fig. 1). Until October 2004, drinking water was supplied to this city exclusively from local wells (mainly wells A–E), whereas well H mainly supplied the suburb Morasha with 15,000 inhabitants, located in close proximity to the military plant.

In August 2004, water samples (in duplicates) were sent for assessment of perchlorate levels to two laboratories in the United States, Knoxville, Tennessee, and Savannah, Georgia. The following results were reported: the well that supplied Morasha had a perchlorate concentration of 684 μg/L as reported by the laboratory in Savannah and 1100 μg/L as reported by the laboratory in Knoxville. The wells supplying the other neighborhoods in Ramat Hasharon had perchlorate water concentrations in the range 63–88 μg/L (Savannah laboratory) and 50–62 μg/L (Knoxville laboratory). Upon receiving these results, the Israeli Ministry of Health ordered an immediate closure of the well in Morasha, whereas the other wells remained active until July 2005. A second set of water samples was taken from these wells on October 4, 2004, and the perchlorate

FIG. 1. Map showing well H, which was the primary drinking water source for Morasha (light gray area at the bottom). Wells A through E (remaining area in the figure) supplied the remaining area of Ramat Hasharon.
concentration in the well at Morasha remained 1100 μg/L. The wells supplying the other neighborhoods had perchlorate concentrations of 49–68 μg/L in October 2004, and 42–94 μg/L in March and April 2005. Four tap water samples taken from homes in these neighborhoods in April 2005 had similar concentrations of perchlorate (42–80 μg/L) as determined by the Savannah laboratory. By contrast, only one residential tap water sample in the highest exposure area was assayed for perchlorate before its closure on October 4, 2004, and the concentration was 340 μg/L.

The study population consisted of all singleton newborns born during the period January 1–September 30, 2004, whose mothers resided in Morasha (very high exposure group), the other neighborhoods of Ramat Hasharon (high exposure group). Only newborns who were born in hospitals and were screened by the Israeli National Newborn Screening (NBS) Program for congenital hypothyroidism (>99%) were considered. Newborns from a neighboring city, Hertzlia (with 83,500 inhabitants), with water perchlorate concentrations <2 μg/L in six samples and 2–2.7 μg/L in five samples, served as a control.

**Newborn screening data**

The Israeli NBS Program is a nationwide screening program for congenital hypothyroidism and phenylketonuria administered by the Ministry of Health. All newborns undergo blood sampling drawn by heel stick for T4 and phenylalanine pre-discharge, at the age of 36–48 hours for >90% of newborns. In premature infants, the sampling is done at the age of 1 week. The same routine is held in all hospitals in Israel. All T4 blood levels were assayed as previously described (15–17) at the central laboratory of the Sheba Medical Center, Tel Hashomer.

**Initial exposure assessment**

Figure 1 shows the water supply of Ramat Hasharon with respect to the local wells. A computerized, geo-referenced file of this information was then created (shape-file). All births in Ramat Hasharon during the study period were geo-coded according to maternal residential address. Those infants not geo-coded were located manually. This file of geo-referenced births was then linked to the hospital T4 data using identity number considered. Newborns from a neighboring city, Hertzlia (with 83,500 inhabitants), with water perchlorate concentrations <2 μg/L in six samples and 2–2.7 μg/L in five samples, served as a control.

**Details on drinking water sources in pregnancy**

Telephone interviews with mothers were done to assess actual exposure to perchlorate from drinking water. The question asked was “Which water did you usually drink during your pregnancy (including water for tea, coffee and concentrate)?” The options were “water from the tap,” “filtered tap water,” and “bottled water.” Data were grouped for responses “tap water” and others.

This nonblinded telephone interview was conducted with all mothers in the very high and high exposure groups to determine their habits of drinking water during pregnancy (tap water or bottled water). A comparison of T4 values was done between newborns in the very high and high exposure groups whose mothers drank tap water regularly during pregnancy.

**Serum perchlorate concentrations from blood bank donors**

To assess perchlorate exposure of the population residing in the three areas, serum samples of blood bank donors obtained during January 2003–September 2004 (before closing the well in the high exposure area) were identified from the Magen David Adom (MDA), National Blood Services, and the Israeli National Serum Bank. Perchlorate assay of these samples was done at the Centers for Disease Control (CDC), in a double-blind analysis. The usage of serum samples was approved by the Israeli Ministry of Health.

Serum perchlorate, thiocyanate, nitrate, and iodide were analyzed by using modifications to previously published methods (18,19). Briefly, 0.5 mL of serum was spiked with an isotopically labeled internal standard isotopically labeled perchlorate (Cl13O4−), mixed, and incubated (2 minutes) to allow the internal standard to equilibrate into the sample. Subsequently, serum proteins were precipitated using six volumes of cold (−20°C) ethanol; thus protein-bound iodine was precipitated and only free iodide was measured. Samples were centrifuged (3016 × g, −5°C) for 35 minutes. Supernatant was transferred to a clean centrifuge tube and evaporated to dryness under a stream of nitrogen at 60°C. The sample was resuspended in 1.0 mL of deionized (DI) water and added to a preconditioned C18 SPE cartridge. The breakthrough fraction and a subsequent 1 mL wash of DI water were collected and mixed, and 1 mL was transferred to an autosampler vial. This solution was subsequently analyzed using ion chromatography–electrospray ionization–tandem mass spectrometry. Perchlorate was quantified based on the peak area ratio of analyte to stable isotope-labeled internal standard. Two quality control pools were analyzed in each analytical batch with unknown samples. Reported results met the accuracy and precision specifications of the quality control/quality assurance program of the Division of Laboratory Sciences, National Center for Environmental Health, CDC (similar to rules outlined by Westgard) (20). Excellent analytical precision was found when serum quality control pools were repetitively analyzed for perchlorate. Analytical response was linear across the calibration range (0.05–500 μg/L). Contamination was assessed by lot screening all reagents and analyzing blanks with each batch of unknowns; no contamination problems were identified.

**Statistical analysis**

Statistical analysis was done on SPSS 14. After checking for normal distribution, two-tailed t-tests were used to compare T4 level means. In addition, analysis of variance (ANOVA) was used for mean comparisons with Bonferroni correction. Chi-square analysis was used for nonparametric data. Pearson correlation was utilized on linear data, and the Spearman Rho correlation was employed in nonparametric analysis. A matched control analysis between the high and low exposure groups was also done. p < 0.05 was considered statistically significant.

**Results**

There were 97 eligible newborns in the very high exposure group, 216 in the high exposure group, and 843 in the low exposure group. The concentrations of perchlorate in drinking water, demographic characteristics, birth weight, gestational age of newborns, maternal age, and corresponding neonatal T4 levels in these three groups are shown in Table 1.

At the first stage of the study, T4 levels obtained from the national NBS program for congenital hypothyroidism were
compared between newborns in the three groups. As shown in Table 1, there was no significant difference in T4 levels between the groups as indicated by a p-value of 0.95. These T4 values were normally distributed in each of the three groups (Fig. 2).

Residing in an area with a very high concentration of perchlorate in the drinking water does not necessarily denote high perchlorate consumption. Therefore, we further investigated the specific patterns of tap water use (e.g., drinking, cooking) during gestation by telephone interview, as an indicator of potential perchlorate exposure. Data on 31 mothers in the very high exposure group and 62 mothers in the high exposure group, who drank tap water, were compared with the low exposure group (Table 2). There were no statistically significant differences in T4 levels between these groups.

In addition to perchlorate, we considered the effects of potential confounders on T4 levels in the study population. Neonatal T4 levels did not correlate with maternal age, birth weight, gestational age, or gender.

A matched control analysis was also done. Twenty-five newborns from the very high exposure area, whose mothers drank tap water and for whom there were complete data, were matched by gender, gestational age, and maternal age with

![FIG. 2. Normal distribution of T4 levels in the very high, high, and low exposure groups.](image-url)
newborns in the low exposure group. The mean $T_4$ level of newborns in the very high exposure group was 14.7 (SD 4.2) $\mu g/dL$ and in the low exposure group was 13.5 (SD 3.4) $\mu g/dL$; again exposure did not prove to be a significant determinant of neonatal $T_4$ levels ($p = 0.271$).

Exposure assessment of the populations residing in the very high, high, and low exposure areas was further studied by a double-blind analysis of serum samples from blood bank donors residing in these areas. Figure 3 shows the serum perchlorate levels of blood donors from three proxy populations (residing in the areas corresponding to the three groups). As expected, the serum perchlorate levels of these three proxy populations fall into distinct clusters that correlated well with drinking water perchlorate concentrations from the same areas. Those with the highest serum perchlorate levels ($5.99 \pm 3.89 \mu g/L$) corresponded with the very high exposure group ($\geq 340 \mu g/L$ in drinking water); those with high serum perchlorate levels ($1.19 \pm 1.37 \mu g/L$) corresponded to the high exposure group ($42–94 \mu g/L$ in drinking water); those with the lowest serum levels ($0.44 \pm 0.55 \mu g/L$) corresponded to the controls ($<3 \mu g/L$ perchlorate in drinking water).

Among the blood donors, the difference between serum perchlorate levels of the high and low exposure groups was significant ($p = 0.04$). However, the difference between the very high and low exposure groups was marginally significant ($p = 0.06$), whereas the difference between the very high and high groups was not significant ($p = 0.09$). The lack of statistical significance between the very high and low exposure groups is obviously due to the small sample size in the very high exposure group ($n = 4$).

The potential for inhibition of iodide uptake by the thyroid gland depends on the relative levels of iodide and physiologically relevant competitive inhibitors of iodide uptake (perchlorate, nitrate, and thiocyanate). Therefore iodide, nitrate, and thiocyanate were measured along with perchlorate in the samples from blood donors residing in the combined very high/high (exposed) versus low perchlorate (control) areas. The values (mean ± SD) were as follows: nitrate, 4845 ± 217 and

![Graph showing serum perchlorate levels](chart.png)

**FIG. 3.** Serum perchlorate levels of blood donors residing in areas corresponding to groups A (Morasha), B (Ramat Hasharon), and C (Herzlia/control) during 2003–2004.
4661 ± 1465 μg/L (p = 0.787); thiocyanate, 1906 ± 1552 and 1067 ± 1044 μg/L (p = 0.086); iodide, 3.10 ± 1.25 and 2.24 ± 0.85 μg/L (p = 0.031); and perchlorate, 1.97 ± 2.69 and 0.44 ± 0.55 μg/L (p = 0.045), for the exposed and control populations, respectively. p-values are two-tailed.

Discussion

We report on the association between gestational exposure to perchlorate in drinking water and T4 levels in newborns from Ramat Hasharon, Israel. Serum T4 of newborns whose mothers drank water with perchlorate concentrations in the range of 42 μg/L and above, up to the highest measured level of 340 μg/L, were similar to those of controls even after exclusion of those whose mothers reported drinking bottled water.

Additionally, serum perchlorate analysis was performed by the CDC on blood donors who resided in the three areas corresponding to various exposure levels. These levels, used as a proxy indicator of exposure, were well correlated with these three exposure groups. Despite likely differences between the proxy blood donors and the pregnant study participants, these proxy samples confirm elevated perchlorate exposure in the residents of Morasha and Ramat Hasharon. It should be noted that perchlorate exposure was measured in blood donors (adults), whereas our study population was pregnant women and their newborns. Our findings indicate that even though pregnant mothers consumed drinking water with perchlorate levels mostly in the range 42–94 μg/L and in some at least up to the highest level measured, that is, 340 μg/L, their newborns presented with normal T4 levels.

Other potential confounders that may affect T4 were also measured in blood donors residing in the same areas of the exposed and control population. These donors, used as exposed and control proxy populations, had similar levels of serum thiocyanate and nitrate, while serum perchlorate and iodide levels were significantly elevated in donors residing in the high exposure area.

Iodine intake is important for protecting the thyroid from iodide uptake inhibitors, such as perchlorate. Blount et al. (21) recently found that perchlorate exposure is associated with decreased thyroid function in U.S. women with low urinary iodine. Higher serum iodide levels in the high perchlorate exposure area may modulate any perchlorate-induced inhibition of iodide uptake. A previous study of pregnant women in the coastal areas of Israel indicates iodine sufficiency (urinary iodine median = 143 μg/L, mean = 130 μg/L) (22) based on World Health Organization (WHO) criteria. Another important difference between the current work and the Blount et al.’s study is the study population: we examined thyroid function in neonates, while Blount et al. (21) studied adults and adolescents. Based on differences in iodine intake and life stage for the two studies, our findings do not contradict those of Blount et al. (21).

The critical concern regarding perchlorate contamination of drinking water is the level of exposure that might place sensitive populations at risk. Therefore, it is of the utmost importance to establish a RfD, that is, the dose in mg/(kg body weight · day) that can be tolerated for a lifetime without adverse health effects. The EPA’s risk assessment on perchlorate from 2002 (6) was made prior to the appearance of the peer-reviewed publication of the Greer et al.’s (1) human exposure study, which showed that 7 μg/(kg · day) did not inhibit iodine uptake in healthy adults. A 10-fold safety factor to account for the most sensitive populations applied to this value resulted in the RfD of 0.7 μg/(kg · day) proposed by the NRC (2). Ultimately, the EPA also developed independently an RfD of 0.7 μg/(kg · day) from which they derived their DWEL of 24.5 μg/L. NRC recommended an RfD in February 2005. Gibbs (23) noted that 10 μg/L perchlorate (converted from Gibbs’ original data units of μmol/L in serum corresponds to 6 μg/(kg body weight · day). This value is very close to the NOEL of 7 μg/(kg · day) based on the clinical study of Greer et al. (1) and approximately 10-fold greater than the RfD of 0.7 μg/(kg · day) proposed by the NRC (2). In our study, serum perchlorate levels of nearly 6 μg/L (Fig. 3) were found in subjects residing in the area corresponding to pregnant women in the high exposure group with ≤340 μg/L perchlorate in their drinking water. If we assume a default drinking water consumption value of 2 L/day (24), subjects in this group drank about 680 μg/day of perchlorate. When we divide this value by the default body weight of 70 kg (24), it is revealed that subjects in this group consumed approximately 9.7 μg/(kg · day) or 38.6% greater than the NOEL [7 μg/(kg · day)]. Similarly the high exposure group (drinking water perchlorate levels of 42–94 μg/L) extrapolates to doses of 1.2–2.7 μg/(kg · day), values less than the NOEL, but about 1.7–3.8 times higher than the RfD.

Keeping in mind the concern for fetal and neonatal development, there have been several human studies that testify to the lack of adverse affects in neonatal thyroid function from exposure to perchlorate in drinking water (8–12,25). Most of these considered perchlorate concentrations in the range 6–16 μg/L, that is, lower than the DWEL of 24.5 μg/L.

Of the epidemiological studies examining thyroid function in neonates with perchlorate exposure, one ecological study by Brechner et al. (3) reported significantly higher median thyroid-stimulating hormone (TSH) levels in age-adjusted newborns attributed to perchlorate. However, this study was criticized by Goodman (13) and Lamm (14) on several grounds. Other cross-sectional studies of newborns in Chile and Nevada did not show the differences reported by Brechner et al. (3). Lamm (14) reevaluated the same sampling data used by Brechner et al. (3) and found that the differences they reported were regional differences and not due to exposure.

We note that perchlorate exposure levels in Ramat Hasharon putatively consumed drinking water contaminated with typically 42–94 μg/L, and those from Morasha, ≤340 μg/L (the highest measured level of perchlorate in drinking water) during pregnancy. These levels exceed any threshold value recommended to date and, to the best of our knowledge, rival the highest drinking water exposure levels reported during gestation. Despite these exposures, neonatal T4 levels were in the range of normal and not different from those of infants born to mothers from areas where perchlorate levels were <3 μg/L.

Crump et al. (8) studied the effect of very high perchlorate exposure in drinking water (100–120 μg/L) on thyroid function in schoolchildren. No difference was found in TSH levels or goiter prevalence among lifelong residents from this area compared with those living in a low exposure area (after adjusting for age, sex, and urinary iodine). No presumptive cases of congenital hypothyroidism were detected in those areas with very high to intermediate levels (5–7 μg/L) of perchlorate in drinking water, whereas several cases were detected in control area (perchlorate undetectable). Neonatal TSH levels were significantly lower in the highly exposed group compared with controls; this is opposite to the known pharmacological effect of perchlorate, and of small magnitude. Both our study and the Crump study (8) indicate that perchlorate in drinking water at concentrations as high as 100–120 μg/L does not suppress thyroid function in newborns or school-age children, respectively.

We note that perchlorate exposure levels in Ramat Hasharon (48–92 μg/L) approach those in Tallal, Chile, and the serum...
perchlorate levels in Ramat Hasharon (nd–6 μg/L) approach the serum perchlorate levels (2.2–8.9 μg/L) found in children in Tal- 
tal (26). In a more recent report of the same areas of Chile studied 
by Crump et al. (8), Tellez et al. (12) found comparable thyroid 
function during pregnancy and postpartum pregnant women 
from subjects exposed to various perchlorate concentrations.

The relative resistance of the thyroid gland to perchlorate 
exposure is most likely explained by normal homeostatic mech-


isms of thyroid hormone metabolism. Inhibition of iodine 
uptake via the sodium/iodide symporter (NIS) is only the first 
step in a complex sequence of physiological events that regu-
late thyroid gland function (27), and it is reversible (28). Below 
the threshold for inhibition of iodine uptake, there would not be 
any effect, and some studies have indicated that TSH is 
not affected by long-term exposure to higher perchlorate levels 
(8,29). Lawrence et al. (30) showed that whereas daily consump-
tion of 10 mg perchlorate for 2 weeks significantly decreased 
iodide uptake by the thyroid gland, neither circulating thyroid 
hormone nor TSH concentrations were affected. An occupa-
tional study of healthy male workers (29) showed that the 
thyroid can compensate for long-term exposure to perchlorate 
by increasing the efficiency of iodine uptake. In their physio-


logically based pharmacokinetic analysis of perchlorate inhibi-
tion of iodine uptake in the rat, Clewell et al. (31) emphasized 
that overall risk to the fetus may be less than to the neonate 
because during gestation the fetus can obtain thyroid hor-
mones from the mother. According to Clewell et al. (31), “the 
maternal hormones may compensate for the increased inhibi-
tion seen in the fetal thyroid resulting in less chance of adverse 
developmental effects.” However, the maternal–fetal T4 trans-
fer is not sufficient to prevent the effects of in utero hypothy-
roidism (18). This was demonstrated by very high TSH and the 
lack of epiphysal nuclei in athyreotic newborns of euthyroid 
mothers (18).

A public health goal for perchlorate is prevention of its 
potential to cause neurodevelopmental deficits in newborns 
that might arise from maternal or neonatal hypothyroidism. 
More definitive evidence of the safety of gestational perchlo-
rate exposure in Ramat Hasharon will require further study of 
neurobehavioral development in infants whose mothers were 
exposed to high perchlorate levels during pregnancy. In their 
ecological study of Nevada children, Chang et al. (32) found no 
evidence of increased risk of attention-deficit hyperactivity dis-
order or autism caused by perchlorate contamination of drink-
ing water up to 24 μg/L (the DWEL proposed by the EPA). 
These authors also reported no differences in fourth-grade 
school performance. However, as recognized by Chang et al., 
there were limitations to their study pertaining to diagnostic 
criteria and the ability to ascertain geographic and demographic 
differences and, perhaps more importantly, to data on individ-
ual residence and water consumption during pregnancy. Such 

study require reexamination. J Occup Environ Med 43:305–
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Disclaimer

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