ORIGINAL ARTICLE

Chronic low level trimethyltin exposure and the risk of developing nephrolithiasis

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ABSTRACT

Objectives Nephrolithiasis (kidney stones) is a common disease with the prevalence that is increasing globally. We previously found that trimethyltin (TMT), a by-product of plastic stabilisers, can inhibit the H^+/K^+ ATPase activity in renal intercalated cells and alter urinary pH, which is a known risk factor for nephrolithiasis. In this study, we conducted a cross-sectional analysis to evaluate the impact of chronic low level occupational TMT exposure on nephrolithiasis.
Methods This study included 216 healthy workers with TMT exposure and 119 workers as controls with no TMT exposure. All study participants were administered a questionnaire and underwent a routine clinical examination including an ultrasonographic screening for kidney stones. Exposures were assessed by measuring TMT concentrations in personal air samples, blood and urine. Logistic regression analysis was used to estimate the ORs and 95% CIs for the risk of kidney stones.
Results TMT exposed workers had a higher prevalence of kidney stones (18.06%) in comparison with control workers (5.88%). High TMT concentrations in personal air samples, blood and urines were positively associated with increased prevalence of kidney stones in workers exposed to TMT compared with controls workers (p-trend values=0.005, 0.008 and 0.002, respectively). The length of employment in plants with elevated TMT levels (duration of the exposure) was significantly associated with the increased prevalence of kidney stones (p trend=0.001). The ORs were 2.66 for <3 years, 3.73 for 3–<10 years and 7.89 for 10+ years of employment compared with control workers.
Conclusions To our knowledge, this is the first report to demonstrate that occupational exposure to TMT is a potential risk factor for nephrolithiasis.

INTRODUCTION

Recent outbreaks of nephrolithiasis and acute kidney injury among children in China have been linked to ingestion of milk-based infant formula contaminated with melamine.[1] This recent epidemic of environmental kidney disease highlights the unique vulnerability of the kidney to environmental insults. The prevalence of nephrolithiasis is reported to be increasing globally.[2 3] In the USA, the reported prevalence of kidney stones increased 37% between 1980 and 1994,[4] and currently the lifetime risk of developing kidney stones in the USA is at 6%–12%,[5] affecting approximately 1 in 11 people.[6] There are multiple risk factors associated with the development of renal stones including genetic variation, gender, geographic region, diet, fluid intake and socioeconomic status.[7 8] However, the increased prevalence of nephrolithiasis worldwide largely cannot be explained by these known risk factors, and it has been suspected that environmental exposures could be a potential contributing cause.

Polyvinyl chloride (PVC) is one of the most used plastic materials in the world. At a global level, demand for PVC exceeds 35 million tons per year. PVC has the tendency to decompose upon heating or on prolonged exposure to light due to loss of HCl from the polymer. Thus, during the manufacturing of PVC plastic, chemical additives including heat stabilisers are used to control the properties of the PVC. Methyltins are extensively used as heat and light stabilisers in plastics.[9] It is estimated that over 15 000 tons of methyltin stabilisers are used each year in Europe,[10] and the consumption of methyltin compounds as PVC stabilisers in the USA was approximately 27% of the world market.[11] Methyltin stabilisers are made from monomethyltin and dimethyltin (MMT and DMT) that are synthesised by a direct chemical reaction. During this process, trimethyltin (TMT), a chemical with higher toxicity than MMT and DMT, is also produced as a by-product. Methyltin-stabilised PVC has extensive applications including packaging materials, foils, piping of potable water, waste and drainage water, window frames and coating materials. With increasing use of methyltin stabilisers in PVC production in developing countries, such as in China, a dramatic increase in occupational poisoning accidents has occurred due to acute exposures to methyltin compounds.[12 13] Moreover, leaching of methyltin ingredients from PVC and related materials can contaminate foodstuffs, beverages, drinking water, municipal water and sewage sludge.[9] However, there are currently no regulations concerning methyltin compounds in drinking water, while they are on the EPA's Candidate Contaminant List.[14]

Previous research in the field has focused on studying the life-threatening acute neurological and psychiatric symptoms.[15–21] Other health impacts and chronic effects of methyltin compounds are largely unknown. While the toxicokinetics of methyltins is not understood in humans, we have shown that TMT has a 15-day half life in rats, suggesting that methyltins may persist and accumulate following chronic occupational exposures.[22] We previously reported that over 80% of the poisoning cases involving acute occupational TMT exposures developed hypokalaemia before showing more deleterious neurobehavioural symptoms, and that treatment of hypokalaemia can delay and significantly improve the neurobehavioural symptoms.[12] We subsequently showed that hypokalaemia was likely due to the direct inhibition of H^+/K^+-ATPase by TMT in renal intercalated cells.[13] The inhibition of renal H^+/K^+-ATPase by TMT can disrupt the regulation of urinary pH and alter electrolyte concentrations and deposition in the kidney and urinary tract, which are known risk factors for crystal deposition and kidney stones formation.[23]

To examine the possible health impact of chronic TMT exposure on the risk of developing nephrolithiasis, we conducted a cross-sectional study with 216 TMT exposed workers and 119 unexposed controls.

METHODS

Occupational setting

Guangdong Province in China is located in the southeastern of China, and has become a manufacturing hub during the last 30 years. From 1994 to 2008, there were at least 20 published reports of acute occupational accidents involving methyltin exposures in this region[12 13] (figure 1). We identified two plants located in the city of Qingyuan, Guangdong, which use methyltins as the heat stabiliser for PVC production to manufacture plastic window blinds. During the last couple of years, three accidents involving acute methyltin exposures occurred in these plants. With support from the local health department and the administrative team in these factories, we conducted an initial monitoring of TMT levels in the two plants. The TMT air level in these factories ranged from below the limit of detection (LOD, 0.00001 mg/m^3) to 0.0463 mg/m^3. The median concentration of TMT in the air was 0.00365 mg/m^3. In the USA, the occupational exposure limits for methyltins have not been established. The The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits for all organotin compounds, including methyltins, are 0.1 mg/m^3 (permissible concentration-time weighted average; PC-TWA) and 0.2 mg/m^3 (permissible concentration-short term exposure limit, PC-STEL). In China, to protect workers from acute neurotoxicity caused by TMT, it has been recently recommended that the TMT exposure in the Chinese workplace should be reduced to 0.0080 mg/m^3 (PC-TWA) and 0.0160 mg/m^3 (PC-STEL). While initial air monitoring suggests that the workers in the two plants in Qingyuan, Guangdong, were exposed to a range of TMT levels, the exposures were generally below the limits established in the USA and in China. We selected a control population from an air conditioner manufacturing plant located in the same city as plants with TMT exposures. Noise is the known major environmental hazard in this plant. Our initial evaluation indicated that the demographic and socioeconomic characteristics of workers in this plant are comparable with the workers in the plants with TMT exposures. Detailed monitoring and analysis of air collected from the control workplace showed TMT concentrations below the LOD.

Characteristics of study subjects

This study was approved by the Institutional Review Boards at the Guangdong Poisoning Control Center, participation was voluntary and written informed consent was obtained before the study. All exposed workers had to meet one inclusion criteria: they should have worked for at least the previous 3 months in the same plant. Exclusion criteria for both TMT exposed and control workers were a history of neurobehavioural disorders, being previously diagnosed with kidney disease, as well as previous occupations with notable exposure to lead, cadmium and other metals, which are associated with an increased risk of nephrotoxicity. A total of 223 manufacturing workers were recruited from the two plants with TMT exposures. Only one worker did not meet all the criteria and was excluded from the study. Of the 222 workers who agreed to participate in the study and signed the consent form, 216 workers participated in the clinical examination, completed the entire questionnaire and provided blood and urine samples. All 119 manufacturing workers recruited from the control factory met the selective criteria, finished the questionnaire and the clinical examination. Thus, the participation rates for exposed and control groups were 97% and 100%, respectively. On the scheduled dates for clinical examinations, interviewers, physicians, ultrasound technicians and registered nurses from Guangdong Poison Control Center (Guangdong Province Hospital for Occupational Disease Prevention) went to the factories and conducted the interview and clinical examination. All participants were assigned a unique identification number and administered a questionnaire

Figure 1 Methyltin poisoning accidents reported in Guangdong, China (1994–2008). Red dots indicate the accident locations during 1994–2008, and the present investigation was conducted in the City of Qingyuan marked by the blue circle.

by trained interviewers requesting information on their demographic characteristics, occupational history, environmental exposures, medical history and current medication use. Both exposed and control workers in the study underwent a routine clinical examination including ultrasonography screening for kidney stones. Ultrasonographic results were later interpreted by physicians who were blind to the exposure status of the individual, as only an assigned identification number was associated with each participant. Two diagnostic criteria were used to define the presence of nephrolithiasis, (1) direct visualisation of the stone on the ultrasonography and (2) the presence of stones ≥4 mm in diameter. At the end of one work shift (8 h), 10 ml of blood with or without anticoagulant and 20 ml urine were collected from all study participants.

Exposure assessment and measurement of air, urinary and blood plasma TMT by gas chromatography-mass spectrometry

Although no TMT was detected in the air of the control plant, all study subjects in the TMT exposure and control factories carried the OSHA Versatile Personal Air Sampler to determine the individual TMT exposure levels in an 8 h work shift. Personal air samples, plasma and urine were analysed for TMT using the gas chromatography-mass spectrometry method previously described.[24] Each collected specimen was given an identification number, which did not include any information about the exposure status of the individuals. The laboratory technicians who performed the TMT analyses were thus blinded to the exposure status of the individuals who provided the specimens. Briefly, following extraction and derivatisation of the collected air, plasma and urine samples, a 1.0 μl sample was analysed using an Agilent 6890N gas chromatograph connected to an Agilent 5973 MSD mass spectrometer with a chemical ionisation source (Agilent, USA). The relative extraction efficiency was 91.5%–101.9%.

Statistical analysis

The t test for continuous variables or Fisher exact test for categorical variables was used to compare the differences between TMT exposed and non-exposed groups. Logistic regression analysis was used to estimate ORs and 95% CIs for kidney stones relative to potential risk factors. All models were adjusted for age and gender in the analysis. Trend tests were performed by including the ordinal variable in the model. TMT exposure levels at the workplace (individual TMT air levels) and urinary TMT concentrations were categorised into low- and high-groups based on the median levels among exposed workers, while blood TMT concentrations were categorised into low (below LOD) and high (above LOD) groups due to a large number of workers with a TMT level below the LOD. The length of employment was categorised into three similar-sized groups, 3 months–<3 years, 3–10 years and >10 years. All statistical tests were two-sided and considered statistically significant for $p < 0.05$. Statistical analyses were conducted using SAS software V.9.3 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

Demographic and TMT exposure characteristics of study participants are summarised in table 1. The median (10th, 90th percentile) individual TMT air levels collected from personal samplers in the methyltin-containing window curtain plants was 0.013 (0.008, 0.028) mg/m^3, expressed as an 8 h time-weighted average. Workers from the window curtain plants had mean plasma TMT and creatine adjusted urine TMT levels of 0.016 μg/ml and 12.73 μg/g creatine, respectively. The spearman correlation coefficient between the individual TMT air levels and the levels of TMT in paired plasma and urine specimens was 0.49 and 0.26, respectively. A relatively good correlation of 0.79 was found between the levels of TMT in paired plasma and urine specimens. All specimens (air, plasma and urine) obtained from subjects in the control air conditioner plant had TMT levels below the LOD (table 1). Exposed workers from the window blind plants were older than non-exposed workers (mean age 36 vs 29 years). There were more male than female workers in both groups (table 1).

Clinical and laboratory examination results from all subjects are presented in table 2. Relative to control workers, the TMT exposed workers were more likely to have certain clinical symptoms or abnormal laboratory tests, including hypertension, gallstones, kidney stones, abnormal ECG, low haemoglobin count, elevated aspartate aminotransferase activity and urine occult blood. Hepatomegaly was the only condition that was significantly higher in the control group (5.04%) than in the TMT exposure group (0.46%). The prevalence of kidney stones determined by abdominal ultrasonography was 18.06% in TMT exposed workers, which was threefold greater than that of control workers (5.88%) ($p<0.01$).

Statistically significant positive associations were observed for the risk of kidney stones with increased TMT levels in personal air samples, blood and urine (table 3). Compared with non-exposed control workers, ORs for kidney stones were 2.87 and 4.10 for workers with TMT air levels below and equal to or above the median level of 0.013 mg/m^3, respectively (p trend=0.005). Similarly, ORs were 2.45 and 5.67 for exposed workers with blood TMT concentrations below and

Table 1 Demographic and TMT exposure characteristics of study participants

Trimethyltin (TMT) exposure	Study subjects (n)	TMT air level (mg/m^3)†	Blood plasma TMT level (μg/ml)	Urine TMT adjusted for creatine (μg/g Cr)	Age* (years)	Gender* Male	Female
Controls	119	Below LOD‡	Below LOD	Below LOD	29.07±7.42§	115 (96.64)¶	4 (3.36)¶
Exposed	216	0.013 (0.008, 0.028)**	0.016 (Below LOD, 0.264)††	12.730 (Below LOD, 211.817)††	36.18±6.83§	152 (70.37)¶	64 (29.63)¶

*p<0.05.
†An 8-h time-weighted average based on arithmetic mean of individual air exposure measurements.
‡Limit of detection (LOD) (0.00001 mg/m^3).
§Mean±SD.
¶Subject number (%).
**Median value of personal TMT air exposure level (10th, 90th percentiles).
††Mean (range).

Table 2 Symptoms and abnormal laboratory test results from clinical examinations among study participants

Symptoms and laboratory test	Control (119 subjects) Number of subjects	%	TMT exposure (216 subjects) Number of subjects	%
Blood pressure				
Prehypertension (systolic, >120 and ≤140 mm Hg)	4	3.36	1	0.46
Hypertension (systolic, >140 mm Hg)**	0		13	6.02
Abdominal ultrasonography				
Fatty liver	9	7.56	8	3.70
Hepatomegaly**	6	5.04	1	0.46
Gallstones in the bile duct*	3	2.52	19	8.80
Kidney stones**	7	5.88	39	18.06
Splenomegaly	2	1.68	4	1.85
Renal cyst	1	0.84	8	3.70
Electrocardiography				
Abnormal ECG**	3	2.52	22	10.19
Blood count				
Low white blood cell count (<4×109/l)	8	6.72	8	3.70
High white blood cell count (>10×109/l)	2	1.68	13	6.02
Low red blood cell count (male <4×1012/l, female <3.5×1012/l)	0		2	0.93
High red blood cell count (male >5.9×1012/l, female >5.5×1012/l)	9	7.56	11	5.09
Low haemoglobin count (male <130 g/l, female <120 g/l)***	2	1.68	34	15.74
High haemoglobin count (male >162 g/l, female >152 g/l)	9	7.56	20	9.26
Liver function				
Alanine aminotransferase (>40 U/l)	6	5.04	14	6.48
Aspartate aminotransferase (>41 U/l) **	5	4.20	39	18.06
Urinalysis				
Urine occult blood*	2	1.68	16	7.41
Protein	3	2.52	3	1.39
Ketone bodies	0		4	1.85

* p<0.05, ** p<0.01 and *** p<0.001.
TMT, trimethyltin.

Table 3 Associations of TMT exposure at the work place (personal air level), blood and urinary TMT concentrations, and length of employment in plants with TMT exposure with the risk of developing kidney stones relative to controls in an air conditioning plant

	Number of subjects	OR (95% CI)*	p Trend
Individual TMT air exposure levels (mg/m^3)†			
Controls (<LOD)	119	1	0.005
Low, <0.013 mg/m^3	135	2.87 (1.04 to 7.92)	
High, ≥0.013 mg/m^3	81	4.10 (1.52 to 11.04)	
Blood TMT levels (μg/ml)			
Controls (<LOD)	119	1	0.008
Low, < LOD	155	2.45 (0.90 to 6.65)	
High, ≥ LOD	61	5.67 (2.03 to 15.87)	
Urine TMT levels adjusted for urinary creatine (μg/g Cr)			
Controls (<LOD)	119	1	0.002
Low, <3.30	108	2.58 (0.94 to 7.10)	
High, ≥3.30	108	4.40 (1.68 to 11.51)	
Length of employment in the plants with TMT exposure			
Controls, 0 years	119	1	0.001
3 months—<3 years	67	2.66 (0.93 to 7.65)	
3–<10 years	73	3.72 (1.30 to 10.67)	
≥10 years	76	7.89 (2.21 to 28.15)	

*Models were adjusted for age and gender.
†An 8-h time-weighted average based on arithmetic mean of individual TMT air exposure measurements.
LOD, limit of detection; TMT, trimethyltin.

Table 4 Associations of TMT exposure in the work place (personal air level), blood and urinary TMT concentrations, and length of employment with risk of developing kidney stones among TMT exposed workers

	Workers without kidney stone (n=177)	Workers with kidney stone (n=39)	OR (95% CI)*	p Value
Personal TMT air exposure levels†				
Low, <0.013 mg/m^3	112	23	1.00	
High, ≥0.013 mg/m^3	65	16	1.32 (0.58 to 3.04)	0.51
Blood TMT level				
Low, <LOD	131	24	1.00	
High, ≥LOD	46	15	2.15 (0.92 to 5.02)	0.08
Urine TMT levels adjusted for urinary creatine (μg/g Cr)				
Low, <3.30	94	14	1.00	
High, ≥3.30	83	25	1.65 (0.79 to 3.42)	0.18
Length of employment‡				
3 months-<3 years	58	9	1.00	
3–<10 years	61	12	1.42 (0.54 to 3.70)	0.53
≥10 years	58	18	3.35 (1.03 to 10.94)	0.04
			p trend=0.05	
Continuous per year			1.07 (0.99 to 1.17)	0.10

*Models were adjusted for age and gender.
†An 8 h time-weighted average based on arithmetic mean of individual TMT air exposure measurements (the range).
‡Median length (10th, 90th percentiles).
LOD, limit of detection; TMT, trimethyltin.

equal to or above LOD, respectively (p trend=0.008), and ORs were 2.58 and 4.40 for exposed workers with urine TMT concentrations below and equal or above the median level of 3.30 μg/g Cr (p trend=0.002). The length of employment at the window blind plants with TMT exposures was also strongly positively associated with the development of kidney stones (p trend=0.001) with ORs of 2.66 (95% CI 0.93 to 7.65), 3.72 (95% CI 1.30 to 10.67) and 7.89 (95% CI 2.21 to 28.15) for workers employed at the plant for <3 years, 3–<10 years and 10 or more years compared with non-exposed control workers, respectively.

Associations of kidney stones with the magnitude of exposure to TMT were similar, but generally weaker, when the analysis was restricted to TMT exposed workers from the window blind plants (table 4). In a comparison of exposed workers with high versus low TMT levels, the OR was 1.32 (95% CI 0.58 to 3.04) for high TMT exposure at the workplace (personal air level), 1.65 (95% CI 0.79 to 3.42) for urine levels and 2.15 (95% CI 0.92 to 5.02) for blood levels. The length of employment (years worked at the plant) was marginally significantly associated with kidney stones (p trend=0.05). Compared with workers with <3 years of employment, ORs were 1.42 (95% CI 0.54 to 3.70) for those employed 3–<10 years and 3.35 (95% CI 1.03 to 10.94) for those employed 10 or more years at the plants.

DISCUSSION

The prevalence of renal stones in adults has increased significantly in recent years;[3 4] however, the factors contributing to this change are unclear. Evidence suggests that environmental, rather than genetic, factors may contribute to the relatively recent increase in the prevalence of this disease.[2 3] In this cross-sectional analysis of workers with or without TMT exposures, we observed that workers with a relatively low level of occupational TMT exposure were more likely to have kidney stones. This condition was especially prevalent among those with a long duration of employment in the window blind plant, which suggests that long-term chronic occupational and potentially environmental TMT exposures may have nephrotoxic effects that warrant further investigation.

There has been an increase in the prevalence of kidney stones in the USA and other countries and currently about 9% of Americans will develop kidney stones at some time in their life.[6] In China, although there are no national data available on the prevalence of kidney stones, the prevalence in Guangdong Province, a heavily industrialised region where this study was conducted, was estimated to be 5%–8%.[25] We showed that the non-exposed workers from an air conditioner plant had a kidney stone prevalence of 5.88%, being very close to the average prevalence rate in the region. However, TMT exposed workers from the window blind plant had a 18.06% prevalence of kidney stones, which was about threefold higher than the non-exposed reference group. More importantly, when adjusted for age and gender, the presence of kidney stones was significantly associated with TMT levels in the personal air samples from the workplace, and with TMT levels in the blood and urine. In addition, chronic TMT exposure, represented by years employed at the plants with TMT exposures, appears to be a strong factor for increasing the prevalence of kidney stones. While a previous rat study has indicated that acute TMT exposure may compromise renal function,[26] this is the first study to demonstrate an association between TMT exposure in the workplace and an increased risk of nephrolithiasis.

Besides the increased prevalence of kidney stones, the prevalence of hypertension, gallstones, abnormal ECG, low haemoglobin count, elevated liver aspartate aminotransferase activity and urine occult blood were also significantly higher in TMT exposed workers compared with non-exposed workers. To the best of our knowledge, this is also the first study to report a number of chronic health effects associated with human exposures to TMT or other methyltin compounds. However, these findings need to be confirmed by other studies.

The main application of methyltin compounds is to make methyltin mercaptide heat stabilisers for processing PVC. Methyltin-stabilised PVC has a wide range of applications including packaging material, piping of portable water and drainage water, window frames and coating materials. The unconjugated methyltin compounds, for example, MMT, DMT and TMTs, can be leached from various methyltin-stabilised

PVC materials. For example, studies have examined the extraction (leaching) of organotin stabilisers from commercial PVC pipes into flowing water and found that an initial concentration of organotin in water can reach as high as 35 μg total tin/litre of water (Sn/l).[27] The leaching of organotins are then reduced and keep at a constant rate of release of about 1 μg Sn/l.[9] With the widespread use of PVC pipes in water transportation systems, methyltin compounds can now be found in various environmental media and ecosystems.[9 28 29] For example, a study showed that organotin levels in residential drinking water using PVC pipes was 0.49 μg Sn/l.[30] The level of organotin compounds (including TMT) in a drinking water reservoir can be up to 0.38 μg Sn/l, while 0.02 μg Sn/l were found in a river downstream from this reservoir.[29] Thus, the widespread use of methyltin-stabilised PVC heightens concerns of the nephrotoxic potential posed by occupational and environmental exposures.

The current study has some limitations that need to be addressed in future studies. The TMT exposure levels at the workplace (air level) and the TMT in blood and urine were assessed at one-time point, and this may not reflect exposures throughout the year or consider that the employees may work in several locations within the plant on an as needed basis during a given day or month. However, a significant positive trend for kidney stones was observed for those with higher exposure measures compared with those with lower exposure levels. The study did not collect other information such as diet and height and weight (body mass index) and so these factors could not be included in the multivariable-adjusted analyses. Future studies should be designed to have a more accurate exposure assessment, including multiple measurements and time points and more detailed history of worker tasks, and other factors which can modify exposure. In addition, given the small scale and exploratory nature of this study, the investigation was focused on kidney stones, but clearly it would be useful to include other tests and parameters that can comprehensively evaluate the status of the kidney and the entire renal system.

In summary, this study provides evidence that occupational TMT exposure was associated with an increased prevalence of kidney stones. Positive associations were observed between TMT exposure levels at the workplace or length of employment and the development of kidney stones. These results suggested that long-term occupational TMT exposures at low air levels, relative to the national recommended permissible standards, may increase the risk of developing kidney stones. Future larger and more comprehensive studies are needed to confirm these findings.

What this paper adds

- ▸ The prevalence of nephrolithiasis (kidney stones) is increasing over time globally and environmental exposures have been suggested to be a contributing cause.
- ▸ Trimethyltin (TMT) exposure inhibits H^+/K^+ ATPase and leads to an increase of urinary pH levels, which is a known risk factor for nephrolithiasis. However, the association between TMT exposure and nephrolithiasis is unclear and has not been previously investigated.
- ▸ Workers with TMT exposure showed an increased risk of developing nephrolithiasis. A significant positive trend was observed for an increased prevalence of nephrolithiasis with increased TMT exposure levels and length of employment in plants with elevated TMT air levels.
- ▸ TMT should be considered as a potential risk factor for nephrolithiasis and other nephrotoxicity.

Contributors XT and XR contributed to the conception and design of the work and to the writing of the manuscript. XT, NL, LK, BW, GL, AY, XR, HG, HZ, YG, JZ and ZL performed the epidemiological investigation. XR, ZG, LK and AMD performed the data analysis and commented on the manuscript. JRO contributed to the writing and commented on the manuscript.

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REFERENCES

1 Dalal RP, Goldfarb DS. Melamine-related kidney stones and renal toxicity. *Nat Rev Nephrol* 2011;7:267–74.
2 Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol* 2010;12:e86–96.
3 Goldfarb DS. Increasing prevalence of kidney stones in the United States. *Kidney Int* 2003;63:1951–2.
4 Stamatelou KK, Francis ME, Jones CA, *et al*. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int* 2003;63:1817–23.
5 Lieske JC, Pena de la Vega LS, Slezak JM, *et al*. Renal stone epidemiology in Rochester, Minnesota: an update. *Kidney Int* 2006;69:760–4.
6 Scales CD Jr, Smith AC, Hanley JM, *et al*. Prevalence of kidney stones in the United States. *Eur Urol* 2012;62:160–5.
7 Srivastava T, Alon US. Urolithiasis in adolescent children. *Adolesc Med Clin* 2005;16:87–109.
8 Walker V, Stansbridge EM, Griffin DG. Demography and biochemistry of 2800 patients from a renal stones clinic. *Ann Clin Biochem* 2013;50:127–39.
9 Hoch M. Organotin compounds in the environment—an overview. *Appl Geochem* 2001;16:719–43.
10 Dobson S, Howe PD, Floyd P. Mono- and disubstituted methyltin, butyltin, and octyltin compounds *Concise international chemical assessment document*: International Programme on Chemical Safety. 2005. http://www.inchem.org/documents/cicads/cicads/cicad73.pdf (accessed on Feb. 2012).
11 Kroschwitz J, Howe-Grant M. Tin compounds. Thioglycolic acid to vinyl polymers. *Kirk-Othmer encyclopedia of chemical technology*. In: Arza Seidel (ed.), New York, NY: John Wiley & Sons, 1997:122–61.
12 Tang X, Xia L, Chen J, *et al*. Clinical analysis on 76 cases from 13 poisoning accidents caused by trimethyltin chloride. *Chin Occup Med* 2008;35:91–4.
13 Tang X, Yang X, Lai G, *et al*. Mechanism underlying hypokalemia induced by trimethyltin chloride: Inhibition of H+/K+-ATPase in renal intercalated cells. *Toxicology* 2010;271:45–50.
14 EPA. Chemical Contaminant Candidates Lists. In: Agency USEP (ed.) 2003. http://water.epa.gov/scitech/drinkingwater/dws/ccl/ccl2.cfm (accessed on Jun 2012).
15 Appel KE. Organotin compounds: toxicokinetic aspects. *Drug Metab Rev* 2004;36:763–86.
16 Kimbrough RD. Toxicity and health effects of selected organotin compounds: a review. *Environ Health Perspect* 1976;14:51–6.
17 McCollister DD, Schober AE. Assessing toxicological properties of organotin Compounds. *Environ Qual Saf* 1975;4:80–95.
18 Seinen W, Vos JG, Van Spanje I, *et al*. Toxicity of organotin compounds. II. Comparative in vivo and in vitro studies with various organotin and organolead compounds in different animal species with special emphasis on lymphocyte cytotoxicity. *Toxicol Appl Pharmacol* 1977;42:197–212.
19 Penninks AH, Seinen W. Toxicity of organotin compounds. IV. Impairment of energy metabolism of rat thymocytes by various dialkyltin compounds. *Toxicol Appl Pharmacol* 1980;56:221–31.
20 Qian YL, Tang HF, Wang YH, *et al*. [Biological monitoring of workers exposed to trimethyltin chloride]. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2008;26:461–4.
21 Rey C, Reinecke HJ, Besser R. Methyltin intoxication in six men; toxicologic and clinical aspects. *Vet Hum Toxicol* 1984;26:121–2.
22 Tang X, Wu X, Dubois AM, *et al*. Toxicity of Trimethyltin and Dimethyltin in Rats and Mice. *Bull Environ Contam Toxicol* 2013;5:626–33.
23 Wagner CA, Mohebbi N. Urinary pH and stone formation. *J Nephrol* 2010;23(Suppl 16):S165–9.
24 Wu B, Xie Y, Rong W, *et al*. A GC-MS based method in measuring trimethyltin in plasma *Chin*. *Occup Med* 2011;38:250–5.
25 Dai M, Zhao A, Liu A, *et al*. Dietary factors and risk of kidney stone: a case-control study in southern China. *J Ren Nutr* 2012;23:e21–8.
26 Robertson DG, Kim SN, Gray RH, *et al*. The pathogenesis of trimethyltin chloride-induced nephrotoxicity. *Fundam Appl Toxicol* 1987;8:147–58.

27 Wu W, Roberts RS, Chung YC, *et al*. The extraction of organotin compounds from polyvinyl-chloride pipe. *Arch Environ Contam Toxicol* 1989;18:839–43.
28 Richardson R, Edwards M. Vinyl chloride and organotin stabilizers in water contacting new and aged pvc pipes: Water Research Foundation. 2009. http://www.waterrf.org/PublicReportLibrary/2991.pdf (accessed on Feb 2012).
29 J Liu J, Jiang G, Liu J, *et al*. Evaluation of methyltin and butyltin pollution in Beijing Guanting reservoir and its downriver Yongding river. *Bull Environ Contam Toxicol* 2003;70:219–25.
30 Sadiki AI, Williams DT. A study on organotin levels in Canadian drinking water distributed through PVC pipes. *Chemosphere* 1999;38:1541–8.

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