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Abstract Extensive uses of methyltin compounds in polyvinyl chloride (PVC) production have led to a dramatic increase of occupational-related methyltin poisoning accidents and the widespread contamination of methyltins in various environmental media. Here, we conducted studies to compare the acute toxicity induced by trimethyltin (TMT) and dimethyltin (DMT), and investigated the cumulative toxic effects of TMT in rats and mice. Neurobehavioral changes were observed in rats and mice treated with either DMT or TMT, but we also observed that both TMT and DMT exposure in rats significantly lowered the blood potassium level. Moreover, the cumulative toxic coefficient factor of TMT was 1.7 in rats versus 3.8 in mice, suggesting a high cumulative risk for rats and a moderate risk for mice. In summary, we demonstrated that acute and chronic exposure to methyltin compounds induced neurotoxicity and hypokalemia. Moreover, our study suggests that TMT can accumulate in the body and pose a risk for workers chronically exposed to a low dose of TMT.

Keywords Acute toxicity · Cumulative toxicity · Dimethyltin · Hypokalemia · Trimethyltin

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Polyvinyl chloride (PVC) products have been widely used due to their low cost, strength, durability and corrosion resistance (Al-Malack and Sheikheldin 2001). These unique features are largely due to chemical additives introduced during the manufacturing process of these products. Organotin compounds are increasingly used as heat and light stabilizers in PVC products because of their stability and high transparency. There are three major types of tin stabilizers, octyltin, butyltin and methyltin. Methyltin has gradually become the dominant type used in the United States and worldwide. Dimethyltin (DMT) is the principle material used to synthesize PVC heat and light stabilizers. Trimethyltin (TMT) is a low-level byproduct of DMT production. During the past few decades, worldwide production and use of methyltins has increased markedly (Hoch 2001), which has resulted in a dramatic increase of poisoning accidents in the workplace. Since 1998, 1,849 cases of poisoning and 23 deaths have been reported in 67 incidents that have occurred throughout the world (Tang et al. 2008, 2010).

Most previous research in the field has focused on studying the acute toxicity of TMT exposure because TMT was considered the main contributor for poisoning accidents in occupational settings (Tang et al. 2008; Aschner and Aschner 1992; Chang 1990) with its known potential effects in inducing neurotoxicity (Noland et al. 1983; Hashizume 1971). Recent reports, however, suggest that DMT exposure could also contribute to the toxic effects in patients from

these poisoning accidents (Yoo et al. 2007; Jiang et al. 2000). Moreover, a recent in vivo study showed that DMT can be converted to TMT by adding a methyl group (Furuhashi et al. 2008), suggesting a possible role in inducing toxicity by DMT exposure. With the wide-spread use of PVC pipes, there is growing concern that methyltins leached from these materials can contaminate drinking water, food and various ecosystems (Richardson and Edwards 2009; Hoch 2001). For example, the levels of DMT in residential drinking water using PVC pipe can be up to 0.49 μg Sn/L (Sadiki and Williams 1999), and methyltin contaminants (i.e. DMT and TMT) can be up to 0.36 and 0.38 μg Sn/L in the drinking water reservoir and 0.18 and 0.02 μg Sn/L in the downstream river, respectively (Liu et al. 2003). The chronic exposure to TMT or DMT could constitute considerable health risks to the general public. However, information is very limited regarding the cumulative effects of TMT exposure, and the potential effects of DMT-to-TMT conversion on methyltin-induced acute and chronic toxicity. In the present study, we studied the acute and cumulative toxic effects of DMT and TMT in rats and mice. We also studied the DMT-to-TMT conversion in rats, and explored its possible role in DMT-induced toxicity.

Materials and Methods

Dimethyltin dichloride, sodium acetate and sodium tetraborate were obtained from Sigma-Aldrich Co. (St. Louis, MO, USA), and trimethyltin chloride was purchased from Acros Organics (NJ, USA). DMT and TMT were dissolved in 0.9 % saline, and fresh solutions were prepared daily and used for the study. Sodium acetate and sodium tetraborate were used to prepare buffers and used in urine preparation for methyltin species analysis. Specific pathogen-free Sprague–Dawley (SD, 180–220 g) rats and Chinese Kun Ming (KM, 18–22 g) mice were purchased from Guangdong Laboratory Animal Center, China (National certification No. 2006A015). All animals were provided a standard diet and housed in an approved facility with climate control and a 12 h light/12 h dark cycle. Animal test protocols were approved by the Animal Care and Use Committee of Guangdong Poison Control Center (GDPCC) in China.

Concentrations of DMT and TMT in urine samples from rats and mice were measured by gas chromatography-mass spectrometry (GC–MS). GC–MS analysis of the urine samples was performed using an Agilent 6890N gas chromatograph connected to an Agilent 5973 MSD mass spectrometer with a chemical ionization source (Agilent, Santa Clara, CA, USA). The urine samples were prepared for analysis following a standard procedure (Wu et al. 2011). Briefly, 5 ml sodium acetate buffer (pH = 3.9), and 200 μl 1 % sodium tetraborate buffer were added into 5 ml urine samples at room temperature. After mixing, the urine samples were centrifuged at 5,000 rpm for 3 min. The organic phase (upper level) of urine was then collected and 1 μl extract of urine was injected in the splitless mode on a non-polar HP-5ms GC column (60.0 m × 0.32 mm × 1.00 μm) (Agilent Technologies Co. Ltd., Beijing, China). Helium was used as the carrier gas and maintained at a constant flow rate of 2.0 ml/min. The inlet temperature was 250°C. The GC oven temperature program applied was as follows: from 50°C (1 min) to 200°C at 20°C/min. The MS interface temperature was maintained at 200°C. The characteristic ion fragments of the derivatized DMT and TMT were selected and identified in the scan mode. The purity of TMT was 99 % and DMT 97 %. The minimum detection limit was 0.1 μg/g, and the relative recovery and extraction recovery were 84.3 %–104.0 % and 91.5 %–101.9 %, respectively.

To determine whether DMT could be converted to TMT, 10 female SD rats were administered DMT by IP injection. Briefly, after one week of acclimatization, each rat was placed in individual metabolic cages and 24 h of urine collected. DMT was then administered at a dose of 10.0 mg/kg body weight (wt) for 3 consecutive days (days 0, 1, 2) at 10 a.m. Urine samples were collected at 24 h intervals each morning at 9 a.m. for 11 consecutive days (days 0–10). The urinary DMT excretion rate for each rat was calculated by dividing the total urinary DMT μg Sn) excreted by the total dose of DMT administered (μg Sn), and an average rate also was computed for the group. The DMT-to-TMT conversion rate was calculated by dividing the total urinary excreted TMT (μg Sn) by the total dose of DMT administrated.

We investigated the acute toxicity of DMT via gavage and IP injection in rats and mice. In each treatment, 20 female and 20 male animals were randomly grouped into 5 groups with each consisting of 4 male and 4 female animals. The vehicle alone (0.9 % saline) was administered to the control group. As our pilot study indicated that male rats were more tolerant of DMT administered by gavage than female rats, different DMT doses were used in gavage treatment for female and male rats. We treated male rats with doses of 100, 215, 464 and 1,000 mg/kg body wt and female rats with doses of 46.4, 100, 215 and 464 mg/kg body wt via gavage exposure. In IP injection, we treated both male and female rats with doses of 10.0, 21.5, 46.4 and 100 mg/kg body wt. The doses of DMT used in the experiment with mice were 100, 215, 464 and 1,000 mg/kg body wt via gavage exposure and 21.5, 46.4, 100 and 215 mg/kg body wt via IP injection. Each animal was observed for changes of behavior and signs of toxicity at 1 and 3 h after DMT administration and once daily thereafter for 14 days. Mortality/moribundity checks were performed daily. On day 15, rats and mice were euthanized individually in a CO_2 chamber and all organs and tissues were

observed macroscopically. The LD_{50} values were calculated according to the Horn method (Horn 1956).

Acute toxicity of TMT in rats has been reported previously (Hoch 2001). We thus only examined the toxic effects and calculated acute oral LD_{50} with TMT treatment via gavage. Twenty female and twenty male rats were randomly grouped into 5 groups. The control group received the 0.9 % saline vehicle alone. Experimental groups were given doses of TMT at 4.64, 10.0, 21.5, and 46.4 mg/kg body wt. The same numbers of mice were used and the doses of TMT administered via both gavage and IP injection were 1.00, 2.15, 4.64 and 10.0 mg/kg body wt.

To investigate the cumulative toxicity of TMT, 20 rats and mice of each sex were used. Based on the acute LD_{50} of TMT in rats and mice, a dose-escalation approach was used in the study. The first treatment was based on a dose of 0.10 LD_{50} mg/kg body wt, and then TMT was administrated via gavage every 4 days in a dose sequentially increased by 50 % increments; e.g., 0.15 LD_{50} at the second treatment and 0.23 LD_{50} at the third treatment. The treatment was terminated either when 50 % of the animals had died, or the cumulative dose was equal to 5.0 times the LD_{50} (20 days). Brains were quickly removed from rats that were euthanized, as well as from those that died during the study. They were then fixed overnight in 4 % (w/v) paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.4) at 4°C overnight. Post-fixed brains were embedded in paraffin and sectioned to include all major structural landmarks of the brain in each section (e.g., olfactory bulb, striatum, cerebral cortex, hippocampus, thalamus, hypothalamus, brainstem, and cerebellum). The paraffin-embedded brain sections were deparaffinized and rehydrated and then stained with hematoxylin and eosin. An experienced pathologist who was blinded to the treatment allocation conducted the neuropathological assessment by evaluating the paraffin-embedded brain sections. The weekly accumulative LD_{50} ($LD_{50}(n)$) was calculated by dividing the total dose of TMT administered for each animal during the experiment period by the number of animals used (i.e. 20). Using a ratio between $LD_{50}(n)$ and a single dose acute LD_{50}, a cumulative coefficient (Kcum) was determined: $Kcum = LD_{50}(n)/LD_{50}(1)$. The cumulative coefficient Kcum, which characterizes the cumulative properties of compounds, was estimated. The lower the value of Kcum, the higher is the cumulative toxicity of a compound. Depending on the Kcum value, 4 levels of cumulative toxicity were specified, $Kcum < 1$, supermarked; $1 \leq Kcum < 3$, highly-marked; $3 \leq Kcum < 5$, moderately-marked; $Kcum \geq 5$, slightly-marked.

Previously, we showed that over 80 % of patients from occupation-related accidents developed hypokalemia before showing any neurobehavioral symptoms (Tang et al. 2008). We thus measured and compared the levels of blood electrolytes (K^+, Na^+ and Cl^-) post TMT- or DMT-treatment in female rats. A total of 90 female rats were selected and randomly grouped into 9 groups with 10 rats per group. A dose at 10 mg/kg body wt of TMT or 16 mg/kg body wt of DMT was each administered to three groups of rats, and 0.9 % saline was given to the three control groups. Blood was collected from the retro-orbital venous plexus of rats at 1 h, 24 h and 7 days after the initial treatment. Blood levels of K^+, Na^+ and Cl^- were analyzed by a 7080 Automatic Analyzer (Hitachi Co., Tokyo, Japan).

All data were analyzed by SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were determined for urinary methyltin analysis. One-way analysis of variance (ANOVA) was used to evaluate differences among experimental groups (significance at $p \leq 0.05$). Given an equal variance between groups, we used Tukey's test to statistically determine the differences between two given groups after the ANOVA test.

Results and Discussion

Dimethyltin is the principal methyltin compound used in industries, and the concentrations of DMT in the workplace and other environmental media often are higher than TMT. We observed a reduced activity in almost all rats administered DMT via gavage exposure. In female rats, recovery of activity had occurred within 2 h following the 46.4 and 100 mg/kg body wt treatments. The activity of female rats was never recovered in the two higher dose groups (215 and 464 mg/kg body wt), and they continually developed other symptoms, such as body convulsions, stomach distention, blood in eyes and mouth, and bleeding and discharge in vagina. There were no deaths found in female rats from the two lower dose groups, but all female rats died within 4 days in the two higher dose groups. Similar symptoms were found in male rats except that they were more tolerant of the DMT treatment than female rats, and no deaths were observed until the dose was up to 464 mg/kg body wt. All rats were dead at 3 days post-treatment in the dose groups of 464 and 1,000 mg/kg body wt. In the following anatomical examination, we observed significant damage to the digestive tract and liver in both male and female rats treated with high doses of DMT. The response of mice after DMT treatment was similar to that observed in rats. A reduced level of activity and stomach distention were found in all of the DMT dose groups. In the 100 mg/kg body wt group, all the animals were recovered within 1 h. However, we observed severe head tremors and aggressive behavior in two mice treated with 215 mg/kg body wt and in three mice with 464 mg/kg body wt. These effects were more pronounced than those observed in rats. The head tremors in some mice lasted for 4 days and

Table 1 Acute gavage and intraperitoneal (IP) toxicity of DMT and TMT in rats and mice

Methyltin compound	Animal species	LD_{50} mg/kg body wt			
		Gavage		IP	
		Male	Female	Male	Female
TMT	Rat	14.70	14.70	–	–
	Mouse	3.16	4.64	3.83	3.16
DMT	Rat	383.0	147.0	31.6	46.4
	Mouse	316.0	215.0	68.1	59.9

–, no studies were performed

then disappeared, but the symptom lasted until death in some mice. The weights of mice were also reduced significantly in these two dose groups. All mice in the 1,000 mg/kg body wt dose group lost activity completely and died within 12 h. Our experimental LD_{50} values are provided in Table 1.

Similar to the symptoms observed in rats administered DMT via gavage exposure, the symptoms following IP injection with DMT in both rats and mice included reduced activity, stomach distention, body convulsions and blood in the eyes. In rats, the reduced activity in the 10.0 mg/kg body wt group was recovered after 2 h, and no deaths were observed. It took about 24 h to recover for rats treated with 21.5 mg/kg body wt, and two rats had died by 11 days. In the 46.4 and 100 mg/kg body wt dose groups, the first death was observed after 12 h and 2 h post-treatment, respectively. The body weight of the rats was also significantly reduced. In mice, except for one female mouse that died 24 h post-treatment with 46.4 mg/kg body wt, all other mice were recovered at 4 h and 24 h post-DMT treatment with 21.5 and 46.4 mg/kg body wt, respectively. All but one mouse treated with either 100 or 215 mg/kg body wt died within 4 h and 1 h, respectively. In gross anatomical analysis, DMT exposure in both rats and mice caused hemorrhages in the digestive tract and severe hepatic and spleen injury in higher dose groups.

The rat LD_{50} for TMT following exposure via gavage was 14.7 mg/kg body wt, and there was no gender difference (Table 1). This observation was similar to the oral LD_{50} value of 13 mg/kg body wt reported by Hoch (2001). In the 10.0 mg/kg body wt dose group, no adverse effects were observed except for a slight reduction in activity. The reduction in activity was more pronounced in rats treated with 21.5 mg TMT/kg body wt. Other symptoms were found at 24 h post-treatment, including head and whole body tremors, blood in the eyes and mouth and discharge in the vagina. All rats in this group died 5 days after the treatment. We observed severe head and body tremors and complete loss of activity in rats treated with 46.4 and 100 mg TMT/kg body wt. These rats did not recover from these symptoms, and died after 48 h and 24 h of exposure, respectively. No significant damage was found in the digestive tract and liver. The toxic responses to TMT exposure in mice were similar between gavage exposure and IP injection (Table 1). Different exposure routes and gender appeared to have very marginal effects on the acute toxicity of TMT in mice. No other adverse post-treatment effects with 1.00 or 2.15 mg TMT/kg body wt were observed except for the reduced level of activity, which was recovered at 2 h post-treatment. In the 4.64 mg/kg body wt dose group, symptoms included reduced activity level, as well as head and whole body tremors. Most of the mice in this group had recovered at 6 days, except for one mouse that died at 20 h post-treatment. All of the mice died within 12 h when they were treated with 10.0 mg/kg body wt TMT.

We previously showed that hypokalemia, the reduction of K^+ level in blood, was an early symptom in patients who were accidently exposed to high levels of TMT in the workplace (Tang et al. 2008), and that this effect could be due to the inhibition of H^+/K^+-ATPase in renal intercalated cells (Tang et al. 2010). In the current study, results showed that both DMT and TMT exposure could significantly reduce the plasma K^+ level within 1 h post-treatment, with the effect lasting over 7 days and becoming even more pronounced (Table 2). The effect of DMT and TMT in inducing hypokalemia in rats was comparable early in the treatment, but become more pronounced later for TMT treatment compared to treatment with DMT (Table 2). The treatment for patients with hypokalemia is early and continuous potassium supplementation (Tang et al. 2008). We previously found that treatment of hypokalemia in patients with TMT poisoning can delay and significantly decrease the neurobehavioral symptoms (Tang et al. 2008), suggesting an association of TMT-induced neurotoxicity and the reduction of K^+ level in plasma. TMT can easily cross the blood–brain barrier and get into the brain because it is soluble in both water and lipids. H^+/K^+-ATPase in neural cells belongs to *p* type ATPases, which use ATP to drive the active transport of ions across cellular membranes. It has a very similar structure as the H^+/K^+-ATPase in renal cells (Kuhlbrandt 2004). While it is unknown if TMT can inhibit H^+/K^+-ATPase in central neural cells, it is reasonable to expect that TMT may exert similar effects on neural cells as on renal cells. It is known that dysfunction of H^+/K^+-ATPase in neurons can lead to multiple neurological diseases (Poulsen et al. 2010). Further studies are needed to determine the effect of TMT and DMT in inhibition of H^+/K^+-ATPase in neural cells and its role on TMT- and DMT- induced neurotoxicity.

There is a growing concern about the adverse health effects resulting from chronic methyltin exposure in the general public. In the cumulative toxicity study of TMT in rats, the toxic response was first observed on the eighth day

Table 2 Plasma levels of K^+, Na^+, Cl^- in rats exposed to DMT and TMT via IP injection (mean ± SEM, mmol/L)

Time	Control (0.9 % saline)			DMT (16 mg/kg body wt)			TMT (10 mg/kg body wt)		
	K^+	Na^+	Cl^-	K^+	Na^+	Cl^-	K^+	Na^+	Cl^-
1 h	5.68 ± 0.51	147.34 ± 2.38	108.55 ± 3.78	5.04 ± 0.34*	143.50 ± 1.35	106.40 ± 1.07	4.95 ± 0.66*	145.05 ± 2.36	109.13 ± 1.62
1 day	5.37 ± 0.43	146.89 ± 1.27	106.89 ± 1.62	4.79 ± 0.70*	143.40 ± 1.51	103.10 ± 2.64	4.87 ± 1.09	141.00 ± 1.41*	108.67 ± 2.16
7 days	5.00 ± 0.39	141.89 ± 3.32	105.03 ± 4.09	4.31 ± 0.27*	146.40 ± 2.84	103.90 ± 2.60	3.76 ± 0.17**	145.85 ± 5.58	106.82 ± 3.49

Data are the mean ± standard deviation (SD). The value is from at least two independent studies

* $p < 0.05$; ** $p < 0.01$

following TMT administration. Both male and female rats showed changes in behaviors, including increased irritability, screaming, jumping and biting. Seizures also developed in some rats and lasted about 30 s, with symptoms of convulsion, head tremors, and salivation. The first death was observed on the 10th day post-treatment, with 50 % mortality occurring over the next two days. Rat brain tissues were evaluated for neuropathological changes (Fig. 1). Notable pathological changes occurred in the cerebellum and hippocampus of TMT-treated rats compared to control rats (Fig. 1a, b). The cerebellar cortical lesion was characterized by the formation of fat vacuoles (Fig. 1c) and the swelling and necrosis of Purkinje cells (Fig. 1d). Moreover, swelling, necrosis, and nuclear fusion of neural cells in the hippocampus were observed in almost all rats (Fig. 1e). The toxic effects of TMT were first observed on the 13th and 15th day in male and female mice, respectively. The symptoms were similar to those observed in rats. The treatment was stopped on the 17th day, at which time 50 % of the mice had died. We calculated the Kcum value of TMT in rats and in mice. As shown in Table 3, TMT exposure constituted a high cumulative risk in rats (Kcum = 1.7), and a moderate risk in mice (Kcum = 3.8). For comparison, melamine, a contaminant in milk-based infant formula, had a cumulative coefficient Kcum of 4 in mice, also indicating a moderate level of cumulative toxicity (Lin et al. 2011).

Table 4 showed rat urinary concentrations of DMT and TMT before and after DMT treatment from day 0 to 10. DMT and TMT were not detected in urine samples of rats collected before the treatment on day 0. High concentrations of DMT were detected in urine samples during the 3-day period of DMT treatment. TMT also was detected in urine samples from the rats after the treatment, and the highest concentration was found on the second day after two treatments. The TMT concentration in urine reached the highest level after two days of DMT exposure, and then declined slightly on the third day, although one more DMT treatment was administered. Urinary TMT concentration was reduced dramatically after the cessation of treatment, and the amount of TMT excretion from urine was fairly constant after the treatment was stopped (day 4–10) (Table 4). Table 5 showed the DMT excretion rates and the DMT-to-TMT conversion rates. The urinary DMT excretion rates ranged from 22.8 % to 57.7 %, with an average excretion rate of 33.9 %. Based on a method used by Furuhashi et al. (2008), in which the DMT-to-TMT conversion rate was calculated by dividing the total amount of TMT excreted (μgSn) by the total dose of DMT administered (μgSn), the average DMT-to-TMT conversion rate was 0.80 %. According to our unpublished data, the excretion rate of TMT via urine was comparable to DMT. Thus, the relative levels of TMT versus DMT in urine should be a good indicator for the relative level

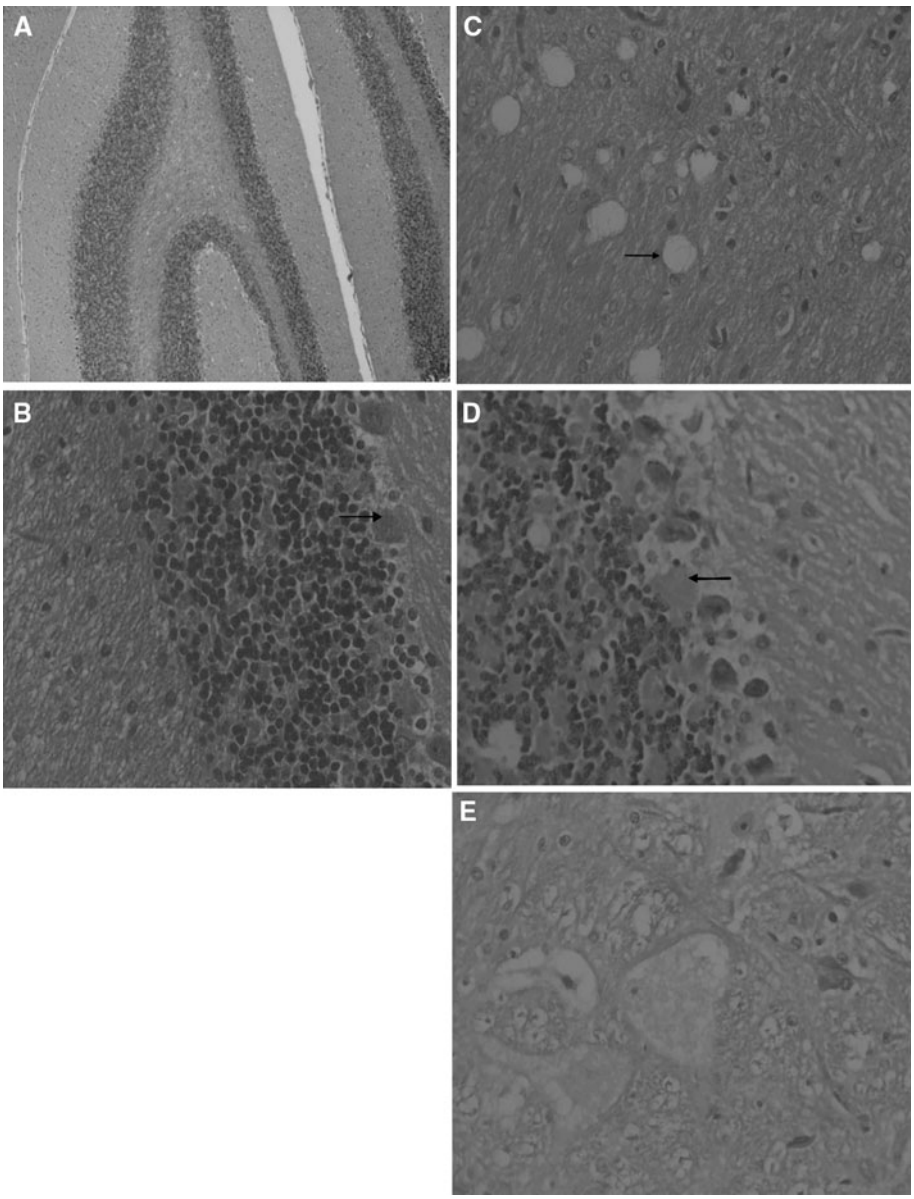

Fig. 1 Histopathological analysis of cerebellum and hippocampus in rats post-TMT treatment (representative images shown). **a**, **b** HE-stained cerebellar cortical section of non-TMT-treated rats with different amplification scales (×40 and ×400, respectively); **c**, **d** the formation of fat vacuoles and the swelling and necrosis of Purkinje cells in cerebellar cortical of rats after TMT treatment (×400); **e** swelling, necrosis, and nuclear fusion of neuron cell in hippocampus of rats after TMT treatment (×400)

Table 3 Cumulative gavage toxicity of TMT in rats and mice

Animal species	Gender	No. of animals	Onset time of symptoms (days)	Time of first death (days)	Time to death of 50 % of animals (days)	Kcum[a]
Rat	Male	20	8	10	11	1.7
	Female	20	8	10	11	1.7
Mouse	Male	20	13	16	17	3.8
	Female	20	15	17	17	3.8

[a] Kcum was calculated as the ratio of the weekly accumulative LD_{50} and a single dose LD_{50}

of TMT versus DMT in blood. We calculated that the TMT comprised an average of 2.42 % of the methyltins in the urine. We know that TMT has a long half-life in tissue and blood, and it can be detected in tissues of rats 80 days post-treatment (our unpublished study). As we reported here that the conversion rate of DMT-to-TMT in rats was about 0.8 % and about 2.4 % of tin in the blood could exist as TMT following the DMT exposure, it suggested that long-term exposure to DMT could lead to an accumulation of TMT in the body.

Table 4 Concentrations of DMT and TMT in the urine of rats post-DMT treatment

Days	Concentration of DMT			Concentration of TMT		
	μg Sn/ml	μg Sn/g Cr	μg Sn/per animal per day	μg Sn/ml	μg Sn/g Cr	μg Sn/per animal per day
0	ND	ND	ND	ND	ND	ND
1	53.00 ± 23.61	27.92 ± 25.45	719.33 ± 316.31	0.92 ± 0.50	0.40 ± 0.17	11.72 ± 4.34
2	66.17 ± 23.50	50.44 ± 44.29	965.95 ± 345.13	1.92 ± 1.08	1.20 ± 0.99	26.14 ± 11.85
3	64.35 ± 44.97	38.96 ± 26.71	982.28 ± 311.95	0.98 ± 0.66	0.57 ± 0.32	15.39 ± 5.61
4	2.87 ± 2.28	1.50 ± 0.67	37.51 ± 22.43	0.18 ± 0.17	0.09 ± 0.05	2.20 ± 1.18
5	0.49 ± 0.25	0.17 ± 0.09	6.67 ± 2.58	0.12 ± 0.04	0.04 ± 0.02	1.70 ± 0.45
6	0.19 ± 0.11	0.07 ± 0.03	2.55 ± 0.75	0.10 ± 0.03	0.05 ± 0.02	1.54 ± 0.52
7	0.14 ± 0.08	0.04 ± 0.01	1.84 ± 0.71	0.10 ± 0.02	0.03 ± 0.01	1.50 ± 0.51
8	0.07 ± 0.04	0.03 ± 0.02	0.89 ± 0.26	0.08 ± 0.03	0.04 ± 0.03	1.32 ± 0.62
9	0.07 ± 0.07	0.04 ± 0.03	0.76 ± 0.19	0.08 ± 0.02	0.05 ± 0.02	1.17 ± 0.48
10	0.05 ± 0.05	0.03 ± 0.03	0.55 ± 0.17	0.08 ± 0.03	0.05 ± 0.03	1.03 ± 0.29

Data are the mean ± SD. The numbers represent the concentration (μg Sn/ml), the concentration relative to creatinine (μg Sn/g Cr), and the amount (μg Sn) of DMT and TMT excreted through urine per animal per day

Cr creatinine, *ND* not detected

Table 5 DMT excretion rates and DMT-to-TMT conversion rates in rats for 11 days ($n = 10$)

Animal no.	DMT excretion (μg)	TMT excretion (μg)	Total given DMT (mg)	DMT excretion rate (% ± SD)	DMT-to-TMT conversion rate (% ± SD)	Ratio of TMT-to-DMT in urine (% ± SD)
1	2,583.83	54.17	7.2	35.89	0.75	2.10
2	2,847.38	84.62	7.2	39.55	1.18	2.97
3	2,053.69	64.00	7.5	27.38	0.85	3.12
4	2,037.33	69.72	7.5	27.16	0.93	3.42
5	4,156.26	75.58	7.2	57.73	1.05	1.82
6	3,003.24	58.14	9.0	33.37	0.65	1.94
7	3,603.54	79.92	9.0	40.04	0.89	2.22
8	2,711.09	53.32	8.7	31.16	0.61	1.97
9	2,065.08	44.68	8.7	23.74	0.51	2.16
10	2,119.62	52.50	9.3	22.79	0.56	2.48
Summary				33.88 ± 10.35	0.80 ± 0.22	2.42 ± 0.56

SD standard deviation

In summary, although the study of toxic effects with chronic exposure to DMT in rats and mice is ongoing in our lab, findings of this current study suggest that long-term exposure to both TMT and DMT could pose significant risks to human health. The long-term effects of methyltin exposure on health in the general population need to be carefully addressed, particularly in consideration of the widespread contamination of methyltin compounds in drinking water systems and other environmental media.

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