Preventable exposure to trimethyl tin chloride: a case report

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Trimethyl tin chloride (TMTC) is a highly toxic organotin compound that affects four main target organs: the brain, liver, immune system and skin. Exposure can occur by inhalation, ingestion or direct skin absorption. Trimethyl tin is but one of many hazardous substances with potentially serious health consequences to which individuals working in research laboratories may be exposed. We report a preventable case of TMTC exposure. Better understanding of the Canadian Workplace Hazardous Materials Information System (WHMIS) legislation and its applicability to the research laboratory situation would prevent such unnecessary exposure to hazardous substances.

Key words: Exposure; hazardous materials; organotin; trimethyl tin.

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Introduction

Research laboratories are often hazardous places. Canadian federal and provincial legislation has been developed to ensure that workers are informed about hazardous exposures in their workplace. This hazard communication programme is known as the Workplace Hazardous Materials Information System (WHMIS). WHMIS regulations related to product supply, distribution and importation are federally implemented; however, the worker–employer aspects of WHMIS are governed by provincial occupational health and labour laws.

The three major components of WHMIS include: (i) product labelling; (ii) material safety data sheets (MSDS sheets); and (iii) worker education. The provision of this education is the responsibility of the employer and, in return, the worker is required to cooperate with and participate in the WHMIS training that is offered. In the case of the research laboratory, it is usually the principal investigator (PI) who is the employer or supervisor and the onus is on that PI to ensure that workers are aware of the occupational hazards in order to prevent health effects of unsafe exposure.

In a study involving 10 PIs and their active wet laboratory facilities in a major teaching hospital, Schweigert et al. [1] compared a walk-through audit of hazards in the laboratory to the PI's report of hazards. They found that radioactive isotopes were the most well-recognized hazard, with complete agreement between PI and audit. However, there were three false negatives for biological agents, one false negative for chemical agents and the majority of PIs did not recognize mechanical/safety hazards, non-radiation physical hazards, or psychological stressors in their laboratories. There were few, if any, policies present to cover the classes of hazard other than radioactive isotopes. Only half of the examined laboratories had training for employees, and of these, it was actually documented in only one.

In this paper, we present a case that illustrates the consequences of this lack of awareness of hazards and the lack of appropriate WHMIS training. We describe a case of trimethyl tin chloride (TMTC) exposure which was preventable, had the hazards been recognized and proper personal protective equipment worn.
Case description

Exposure

Mr K is a 27-year-old male studying chemistry in a university graduate school in Toronto, Canada. He was working on a project to synthesize an antihypertensive agent in which TMTC was mixed with sodium and dimethylethyl ether to form a non-isolated intermediate. This substance was subsequently reacted with 3-bromopyridine and dimethylethyl ether to obtain the final product of trimethyl tin pyridine (3-pyridyl trimethyl tin). He had used the organotin compounds only occasionally, the last time being ~1 year previously. He was aware of only one other laboratory worker who used such compounds, again on an infrequent basis. Mr K said that when he was using the TMTC he was unaware of its toxicity.

Mr K was exposed to TMTC while he measured 15 cm³ (300 mg) of powdered TMTC into a glass flask from its original glass storage container, which was covered with a rubber septum. Although he did wear goggles and latex gloves, a respirator was not worn, nor was this measurement carried out under a fume hood as it should have been. After the TMTC was transferred to the flask, the remaining procedures took place under the hood, preventing ongoing exposure. No air sampling was carried out to estimate the level of exposure.

Symptoms

Although he had no immediate symptoms on exposure, Mr K later developed neurological, respiratory and gastrointestinal symptoms. Within 3 h of exposure, he began to feel agitated. That night, a piercing right-sided temporal headache woke him from sleep. It was associated with dizziness and difficulty focusing his vision, partly due to twitching of his right eye and cheek. He also complained of left foot numbness. He developed cough and difficulty in breathing, characterized by inspiratory discomfort. In addition, he complained of subternal and epigastric burning, with flatulence. Although they did not completely resolve, the symptoms slowly subsided after 5 days, during which time he slept more than usual.

He saw his family physician 2 days after his symptoms started, who advised him that his illness was resolving and should be short lasting. However, his symptoms persisted and he was unable to resume his studies for 5 days. When he returned to the laboratory, he requested further information about the chemicals that he was working with on the day he became ill and their long-term effects. He subsequently discussed his concerns about long-term toxic effects with his family physician and this led to a referral to the Occupational Health Clinic, St Michael’s Hospital, a University of Toronto affiliated teaching hospital.

He was seen there 20 days after exposure and he was still complaining of agitation, headache, right-sided neck tingling, shortness of breath, chest discomfort and abdominal pain, although his symptoms were slowly resolving. He was very anxious about the possibility of developing chronic toxic effects related to the TMTC exposure.

His past medical history was significant for renal calculi and Helicobacter pylori infection, but there was no history of migraine, excessive stress, or psychiatric disorder. He was taking no regular medication prior to his exposure and had no allergies.

On initial examination he was mildly anxious, but neurological and mental status examinations were normal. In particular, there was no evidence of tremor. The only other finding was some mild lower abdominal tenderness, but respiratory and cardiac examinations were both normal.

Investigation and management

Results of laboratory tests carried out 2 days after exposure by his family physician revealed normal complete blood count (CBC), electrolytes (Na, K, Cl), creatinine, alkaline phosphatase, aspartate aminotransferase (AST), total bilirubin, urate, glucose, triglycerides, thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate (ESR) and routine urinalysis. The only abnormal finding was an elevated blood cholesterol level. The CBC, creatinine, AST and total bilirubin were repeated by the occupational health clinic 20 days after exposure and were also normal. No biological monitoring of organotin was attempted after such a long period post-exposure.

Following his initial assessment in the occupational health clinic, the persistence of his symptoms led to a referral to a neurologist and a magnetic resonance imaging (MRI) scan at the time was normal. By 2 months after his exposure he was still not symptom free. He began to notice stiffness in his wrists, arms and back. His abdominal pain persisted and he developed diarrhoea. An upper gastrointestinal series showed impaired gastric emptying, but upper endoscopy and colonoscopy to the caecum were unremarkable. The impression was that of an irritable bowel and he was treated with cisapride 20 mg b.i.d.

In addition, he continued to experience twitching, now of his eyelids and arms. He complained of short-term memory problems and was having particular difficulty retaining new information. Over time, he was referred to three different neurologists, who agreed that Mr K had a normal neurological exam and that his ongoing symptoms were not due to any serious underlying organic cause including chemical exposure, but rather were more likely due to anxiety.

Mr K was referred to a psychiatrist, who initiated
Discussion

Although Mr. K was exposed to extremely toxic TMTC, fortunately his exposure was apparently minimal. Nonetheless, he experienced symptoms consistent with exposure to TMTC (agitation, gastrointestinal symptoms). With time, these symptoms settled, and his persistent symptoms could be explained more appropriately on the basis of anxiety; however, it is not difficult to imagine that his exposure could have easily been much greater, with potentially non-reversible health effects as the outcome.

The diagnosis of initial organotin toxicity is supported by the fact that his symptoms began 3 h after exposure and were those expected from TMTC toxicity. He reported these symptoms to his family physician prior to his knowledge of the actual health effects of TMTC. The differential diagnosis would include a viral illness and primary anxiety disorder. However, the results of the CBC were normal and therefore not consistent with a viral aetiology, and there was no past history of psychiatric disturbance or recent stressful events.

Tin compounds are classified as either inorganic or organic. Because the inorganic tin compounds are poorly absorbed and rapidly excreted, their toxicity is generally low. The organotin compounds, by contrast, are more toxic, the most toxic being the trimethyl and triethyl tins [2], which are comparatively well absorbed from the gastrointestinal tract [3,4]. Toxicity of organotin compounds is high and exposure can occur by inhalation, ingestion or direct skin absorption. Organotin toxicity affects four main target organs: the brain, liver, immune system and skin [5]. The main results of toxicity are skin and eye irritation, diarrhoea, abdominal discomfort, cholangitis of the lower biliary tract with later hepatotoxicity, and neurotoxicity [3].

Trimethyl tin is particularly neurotoxic and acts as an acute excitotoxin at high levels. It causes neuronal necrosis [3], primarily affecting neurons of the limbic system including the hippocampus and entorhinal cortex [6]. Clinically, the manifestations of neurotoxicity include headache, impaired memory and behavioural changes such as aggressiveness, disorientation and psychotic behaviour [7].

The neurotoxic presentation most frequently reported in human cases is an acute limbic–cerebellar syndrome [8–12], the manifestations of which include memory defects, confusion, seizures, tinnitus, insomnia, depression sometimes alternating with rage, incongruous affect and slow paroxysmal EEG recordings. The acute neurological effects may present immediately, although a delayed or latent period of up to 3 days has been reported in several studies [9,12]. Despite a variety of proposed neurotoxic mechanisms, which include reduction in hippocampal zinc levels, elevated extracellular glutamate and decreased γ-aminobutyric acid concentration, the mode of action of trimethyl tin remains unclear [6,9].

Although serum organotin levels have been measured in previous studies [12], the most commonly measured biological sample is urine. Urinary trimethyl tin levels are thought to be consistent with body trimethyl tin burden, with maximum urinary levels occurring within 4–10 days of exposure [9]. Normal mean urine levels of organotin compounds have been previously reported at 0.1 µg/dl [13]. The American Conference of Governmental Hygienists, an organization that publishes yearly documentation of threshold limit values and biological exposure indices (BEIs), lists a 0.1 mg/m³ time-weighted average exposure limit and a short-term exposure limit of 0.2 mg/m³ for organic tin compounds; however, no BEI is listed for biological monitoring [14]. To our knowledge, no other biological monitoring recommendations are available in North America.

Although this graduate student was handling toxic substances, he had not been given specific information about safe handling of the chemicals. He had completed general WHMIS training, but was not instructed specifically on the use of the substances in his laboratory, nor was he told how to handle them safely. WHMIS education has a general component in which the worker learns about the hazards of controlled products and about the WHMIS programme. Perhaps more important is the second training component, in which workers are taught both about the hazards specific to the site where they work and about work procedures such as safe handling, use, storage and disposal of dangerous products.

A successful training programme would provide the workers with the ability to identify the hazardous substances with which they work, to obtain hazard information about those substances, to understand various methods of protection from the hazard and to understand emergency procedures if there has been an exposure. However, training programmes are not always successful [1,15].

Due to the toxicity of the organotin compounds, prevention of exposure is exceptionally important. In this case, Mr. K was wearing only latex gloves and goggles for protection. His personal protective equipment should also have included a respirator and all procedures should have been performed under a fume hood. Fortunately, the short duration of his exposure led to gradual resolution of symptoms, but if the exposure had been longer, e.g. if there had been a spill, the result may have been a totally preventable, but permanent neurological deficit because
organotins are difficult to eliminate from the central nervous system.

This case illustrates the fact that individuals working in research laboratories may be exposed to hazardous substances with potentially serious health consequences, which are preventable with appropriate control measures, work practices and personal protective equipment. The purpose of WHMIS training is to ensure that such hazardous exposures do not occur and thus it should be viewed as an important preventive strategy for employers, including PIs in charge of university and hospital-based research laboratories.

References