Rat poison and food security in the People’s Republic of China: focus on tetramethylene disulfotetramine (tetramine)

Abstract The last several years have seen a large number of mass poisonings in mainland China, particularly those caused by illicit rodenticides. One rat poison, tetramine (tetramethylene disulfotetramine) is responsible for a great percentage of death and injury in the People’s Republic of China (PRC). Tetramine is an acutely toxic substance with human oral toxicity estimated as low as 0.1 mg/kg, and is widely available in open markets in mainland China—this despite being prohibited for manufacture or sale in the PRC. Being a GABA antagonist, and having an extremely potent effect on the brain stem, many victims can quickly fall into convulsions and die within hours following ingestion. With no known effective antidote at this time, clinical data from the PRC show that acute cases of tetramine poisoning are extremely difficult to treat. The widespread use of tetramine—including its reported sale at a Malaysian outdoor market in September 2002—could exacerbate its hazard to public health, particularly in those areas having large overseas Chinese populations.

Keywords Tetramethylene disulfotetramine · Toxicity · Rodenticides · Pesticides · China

Introduction and background

Throughout the 1990s and especially in recent years (2000–2003), mainland China has continued to experience a large number of accidental and deliberate poisonings due to chemical pesticides. During the last decade, public health authorities in the People’s Republic of China (PRC) estimated that there have been 100,000 human cases of pesticide poisonings in China per year (Wu and Liu 2000). This large figure is no doubt due in part simply to China’s very large rural population, and because a significant percentage of its people are engaged in the agricultural sector. It is nonetheless alarming that rodenticides may alone be responsible for up to 70,000 annual poisonings in China. What is more, according to one Beijing-based medical journal, a substantial portion of recent rodenticide poisonings in China have been deliberate (Qiu et al. 2002), in many cases involving the use of a relatively novel rodenticide, tetramethylene disulfotetramine, (tetramine, C₄H₈N₄O₄S₂; CAS no. 80-12-6). The 2002 case described below is among the more recent and striking examples.

In mid-September 2002, after becoming jealous of the business success enjoyed by a rival snack bar (the Zhengwu Pastry Bar in Nanjing), Mr. Chen Zhengping (32) used rat poison to adulterate his competitor’s foodstuffs. Chen used an acutely toxic rodenticide consisting of the active ingredient tetramine. As a result, 42 people died and another 300 customers were poisoned after eating the tainted comestibles. On 16 September 2002, a day following the incident, Chen was caught, while attempting to flee on a train, in Zhengzhou (approximately 600 km northwest of Nanjing). On 14 October 2002, having lost his appeal to a higher court in Jiangsu Province, Chen Zhengping was executed for murder (People’s Daily 2002).

Tetramethylene disulfotetramine: a (not-so) novel rodenticide

In 1949, chemists at Bayer in Germany published the synthesis of tetramine. A year later, incidentally, tetramine was found to be responsible for poisoning a large number of German furniture workers. It happened that the “Crinex” wool used at the time had been made with a resin polymer that formed tetramine as a byproduct during processing (Haskell 1956). Further toxicological investigations discovered that tetramine was many times...
more toxic than strychnine, and one investigator noted in 1952 that the compound’s “high toxicity probably precludes its use as a rodenticide” (Richter 1954) (Fig. 1).

Still, a US patent was issued for the use of tetramine as a rat poison in 1953 (Hecht et al. 1953). In the late 1950s, tetramine was used experimentally to discourage rodents and other scavengers from gobbling up Douglas fir seeds in open fields during reforestation efforts in the United States. However, no known antidote yet exists in the event of accidental poisoning of humans or animals with tetramine. Therefore, the wide application of this compound has been thought unsafe, and tetramine found very limited use in the West.

Tetramine falls into a category of cyclic compounds noted for their high toxicity in mammals (Esser et al. 1991). Tetramine acts directly upon the brain itself, blocking the chloride channel of the inhibitory neurotransmitter receptor of \( \gamma \)-amino butyric acid (GABA). Very small amounts of tetramine, estimated as low as 0.1 mg/kg weight (oral LD\(_{50}\)) in mammals can lead to convulsions and death, with 7.0–10.0 mg/kg dosages considered lethal in humans (Guan et al. 1993); the minimum lethal dose for humans has been estimated at about 5.0 mg/kg. The effects of tetramine can manifest themselves quickly, from about 30 minutes to a few hours following ingestion (Tang et al. 2000). Symptoms of tetramine poisoning include fainting, epileptic seizures, incontinence, and foaming at the mouth. Data compiled from laboratory animal studies are also instructive. One Chinese medical journal described tetramine poisoning in mice the following way: “After ingesting the bait, mice are poisoned acutely. They are excited. Their tails straightened. They jump around, and occasionally screamed. It is followed by periodic or continuous spastic convulsion. Their limbs become stiff. In some cases, this cycle repeats a few times. Then, they die.” (Zhou et al. 1998). Clinical and anecdotal reports from the PRC also noted hemoptysis among some victims of tetramine poisoning, but this symptom and its relationship to the toxicity of tetramine have not yet been satisfactorily explained.

### Persistence in the environment

Tetramine is all the more dangerous due to its high stability in water, making it a relatively persistent environmental contaminant. Early investigators confirmed that tetramine remained equally toxic in water solution 6 weeks after being prepared. Secondary and even tertiary poisonings with tetramine are entirely possible. Roaming dogs that may eat rats poisoned with tetramine, for example, represent a potential threat to certain segments of the Chinese population, as the chemical can remain at toxic levels in the tissues. In one Hangzhou-based newspaper account, for example, a warning was issued concerning suspect dog meat being sold in a local market. (Dushikuaibao 2001).

### Treatment options for tetramine poisoning

Tragically, Chinese physicians have more experience than anyone when it comes to the clinical treatment of tetramine poisoning. However, data are still incomplete as to effective treatment options. Phenobarbital, when administered early, has been able to increase survivability of some victims of tetramine poisoning, while experimental use of vitamin B\(_6\) and sodium dimercaptopropane sulfonate has shown promising results (Qiu et al. 2002).

Despite the large number of cases of tetramine poisoning in the PRC, published clinical studies are somewhat difficult to find in the open literature. One article published in 2001, however, compiled data from 15 cases of tetramine poisoning that were treated in Hunan province (Xiangya Hospital) over the course of a few years (1998–2000). In the authors’ discussion of their experience in treating tetramine poisoning, the physicians noted the importance of gastric lavage for cases of acute poisoning. Secondly, their empirical data suggest that plasma exchange treatment was the next best course of action. “…for 13 patients who exhibited convulsive symptoms, their condition rapidly improved following plasma exchange. Although symptoms returned in some cases 12–24 hours afterwards, convulsions resolved following a second round of plasma exchange.” Finally, the authors emphasized that in acute cases of tetramine poisoning their results showed the need for aggressive therapy using anticonvulsants, therefore requiring an artificial airway: “In securing an airway by intubation, combined with mechanical ventilation, one did not have to be reticent about administering large doses of tranquilizers for anticonvulsant therapy. Furthermore, by doing so one could ascertain whether or not treatment of those critical cases will ultimately be successful.” (Li and Zeng 2001).

### Rodenticides and mass poisonings in China

Except for Tibet, open-source data from all mainland Chinese provinces have recorded major poisoning epi-
sodes involving prohibited rodenticides (Zhou and Deng 2002). From 2000–2002, Henan province alone saw 275 cases of rodenticide poisoning, 63 of these being fatal. Most of these cases involved the rodenticide tetramine, variously sold as Dushuqiang, Sanbudao, and “4-2-4,” among other trade names. According to a Chinese media source, at least 1,000 Chinese citizens died from tetramine poisoning in various incidents during the late 1990s (Xinhua News Agency 2000). In a span of only 10 days during 2000, for example, Henan province saw three separate Dushuqiang poisoning incidents involving 340 people, most of these (305) being middle-school students. Table 1 lists additional representative cases of accidental and deliberate poisonings with rodenticides in the PRC.

In addition to the September 2002 Nanjing incident described above, here are some additional examples:

- On 28 January 2002, in Linxian city, Hunan Province, 120 middle-school students fell ill after consuming cafeteria food that had been deliberately poisoned with tetramine. It was later revealed that a fellow student—who had compiled a long record of truancy—was responsible. The student, angry that the school had informed his father of his unsavory behavior, tried to take revenge on his teacher by scattering tetramine on vegetables in the commissary during after-school hours. Reportedly, the student purchased a pouch of tetramine rodenticide for the equivalent of US$ 0.16. (1 yuan). Although the miscreant intended to poison only the teacher, the tainted ingredients were unwittingly used by the kitchen staff and served throughout the school population (Wang 2002).

- In August 2002, Mr. Zhong Dongxiang of Tongchuan City, Shaanxi Province, plotted to kill his wife so he could marry his mistress from Xi’an, and he purchased some tetramine on the open market. After at least one failed attempt, on 3 October he managed to kill her by poisoning milk that was being regularly delivered to their residence. In the process of doing so, however, he also managed to poison 15 others in the building (presumably due to secondary contamination). As a result of this event, about a ton of milk had to be discarded for fear of further contact with the rodenticide.

- On 26 September 2002, five people died from tetramine poisoning due to the actions of a 17-year-old student named Li Xiang, who was upset after being caught cheating on a test. Li Xiang purchased a pouch of tetramine rodenticide for the equivalent of US$ 0.16. (1 yuan) and poured it into a pot of tea that was being served to the entire student body. Although the student intended to poison only his teacher, the tainted items were unwittingly used by the kitchen staff and served throughout the school population (Wang 2002).

Table 1 Known cases of rodenticide poisonings in China, 1998–2002 (NA not applicable)

| Date                  | Location (province, locale) | Rodenticide | Injuries | Fatalities |
|-----------------------|-----------------------------|-------------|----------|------------|
| August 1998 to February 1999 | Guangdong, Xingning City         | Tetramine   | 29       | 1          |
| April 1999            | Guangxi                      | Tetramine   | 26       | 3          |
| 17 June 1999          | Gansu                        | Tetramine   | 10       | 3          |
| 15 August 2000        | Jiangxi, Nanchang            | Tetramine   | 48       | NA         |
| 14 September 2000     | Beijing                      | Tetramine   | 14       | NA         |
| November 2000         | Chongqing                    | Tetramine   | 53       | 1          |
| 1 January 2001        | Henan, Jiyuan                | Tetramine   | 3        | 1          |
| 6 January 2001        | Shandong, Jinan              | Tetramine   | 67       | 2          |
| 8 January 2001        | Xinjiang, Shihezi            | Tetramine   | 70       | NA         |
| 12 January 2001       | Xinjiang, Shihezi            | Tetramine   | 10       | NA         |
| 30 January 2001       | Hunan, Nanxian               | Tetramine   | 4        | NA         |
| 6 February 2001       | Hainan, Haikou               | Tetramine   | 75       | NA         |
| 9 February 2001       | Gansu, Baiyin                | Tetramine   | 3        | 1          |
| 16 February 2001      | Guangxi, Guanyang            | Tetramine   | 12       | NA         |
| 16 February 2001      | Hainan, Haikou               | Tetramine   | 6        | NA         |
| 16 February 2001      | Henan, Yanshi                | Tetramine   | 6        | NA         |
| 22 February 2001      | Shandong, Dezhou             | Fluoroacetamide | 4     | NA         |
| 24 February 2001      | Henan, Yiyang                | Tetramine   | 17       | NA         |
| 27 February 2001      | Xinjiang, No. 5 Farm Area    | Tetramine   | 200      | NA         |
| 27 February 2001      | Siquan, Nanchong             | Tetramine   | 3        | NA         |
| 6 March 2001          | Liaoning, Fuxin              | Tetramine   | 3        | NA         |
| 7 March 2001          | Jiangsu, Xuzhou              | Tetramine   | 5        | NA         |
| 7 March 2001          | Henan, Qixian                | Tetramine   | 17       | 1          |
| 13 March 2001         | Guangxi, Dahu                | Tetramine (suspected) | 32     | NA         |
| 18 March 2001         | Guangxi, Guixi               | Tetramine   | 4        | NA         |
| 8 August 2001         | Hunan, Ningxiang             | Tetramine   | 94       | NA         |
| 6 November 2001       | Shaxi, Guixian               | Tetramine   | 86       | NA         |
| 23 November 2001      | Guizhou, Sinan county        | Tetramine   | 11       | 8          |
| 28 January 2002       | Hunan, Linxian city          | Tetramine   | 120      | NA         |
| 15 September 2002     | Jiangsu, Nanjing City        | Tetramine   | 300+      | 42         |
| 26 September 2002     | Shaanxi Province, Xi’an      | Tetramine   | NA        | 5          |
| 27 September 2002     | Shaanxi Province, Xi’an      | Tetramine   | 26        | NA         |
| 3 October 2002        | Shaanxi province, Tongchuan City | Tetramine (and other rodenticide) | 15     | 1          |
| 10 November 2002      | Anhui province, Anqing City  | Tetramine   | NA        | 2          |
| 25 November 2002      | Guangdong, Wuchuan City      | Tetramine   | 72        | NA         |
| 13 February 2003      | Sichuan province, Chengdu    | Tetramine   | 5         | 15         |

*Poisoning event is either known or suspected to have been deliberate*
“farm girl” in Xi’an. Reportedly, the young woman admitted to having poisoned food with tetramine at the restaurant where she worked because her boss had held back her pay (Ma 2002).

On 10 November 2002, in Anqing City, Anhui Province, Mr. Jiang Xingyou decided to poison the food of a competing restaurant in the form of a rodenticide. He felt he was stealing away his customers. At informal open markets he purchased tetramine in the form of a rodenticide, and he subsequently adulterated food at the rival eatery—several times. Although it is not known how many people eventually fell ill, two workers at the restaurant died as a result of tetramine poisoning (AFP Hong Kong 2002).

For reasons that included his own failing preschool that he managed—and constant fighting with his wife—Mr. Huang Hu (30) apparently took out his frustrations at a rival school by using tetramine. In the evening of 24 November 2002, Huang snuck into the Kangle (“Happy Health”) No. 2 Kindergarten, and adulterated the table salt in the kitchen. As a result, 70 children and two teachers were poisoned. Chinese authorities claimed Huang later made a full confession (Jian and Zhan 2002).

One should caution, however, that statistics of poisoning incidents in the PRC are incomplete due to various factors, including a tendency on the part of the Chinese government to not fully divulge news on domestic affairs. Whether it is the prevalence of HIV/AIDS among the Chinese population, foot-and-mouth disease in domestic Chinese livestock (referred to officially as “disease no. 5”), or the recent outbreak of the severe acute respiratory syndrome (SARS) virus, there is a past history of reticence on the part of Chinese authorities to be transparent concerning outbreaks of infectious disease and other public health problems (Crodgy 2002). Therefore, open-source data on rodenticide poisonings in China may be erring on the very low side.

The legal and illicit market for rodenticides in China

The worldwide market for rodenticides roughly breaks down into two main categories: acute rodenticides, those that kill relatively quickly, and chronic rodenticides (e.g., anticoagulant types) that may take anywhere from 1 to 10 days and multiple feedings of poisoned bait to achieve their effect. Acute poisons such as hydrogen cyanide, strychnine, and zinc phosphide compounds have traditionally been used to control rodents for many years past. In recent times, however, safer compounds such as the warfarin anticoagulant agents have been adopted for control of mice and rats. The marketability of anticoagulant rodenticides—poisons that kill by causing internal bleeding in mammals—is notably enhanced by the availability of an antidote (vitamin K) in case of accidental exposure of non-target animals (e.g., people, livestock and household pets).

In China, the rural customer has been particularly fond of rodenticides that act quickly, however, including the acutely toxic poisons that have been prohibited by the Chinese government. (These include not only tetramine, but also silatrane, a cyclic, silicon-based compound that was investigated by South African chemical weapons specialists for use in assassinations during the 1980s). These banned rodenticides, mainly tetramine and fluoroacetate, comprise up to 80% of the illicit market for acute rodenticides in China’s rural areas, and 60% overall across the country, according to a Henan-based manager of a chemical firm in the PRC (Huashengbao 2000).

Regulation of pesticides in China: more in the breach than the observance?

Although many pesticides have been regulated in the PRC since the 1950s, illicit manufacturers in China continue to produce not only domestically banned organochlorine compounds such as DDT, but also a number of highly toxic rodenticides (Zhong et al. 2003). Sales of these compounds are often conducted in large open markets with informal marketing and retail distribution networks. This fact, coupled with the very low cost of the final product (starting at US$ 0.10 per unit) makes it easy for the average Chinese citizen to gain access to very toxic substances, including acutely toxic rodenticides such as fluoroacetate, fluoroacetamide, tetramine, and possibly others.

Chinese authorities singled out for prohibition the unregulated use of acutely toxic rat poison fluoroacetamide in 1984, and later fluoracetate as well. Such laws, unfortunately, did not dissuade two individuals in Gaoyao City, Guangdong Province, from using fluoracetate and fluoroacetamide to perpetrate mass murder in 1995. During the spring and summer of that year, acting upon what was later described as “superstitious influence,” Du Runqiong (42) and her son Tang Youhua (20), used these rodenticides to poison and kill 18 people. These individuals used both rodenticides to contaminate rice, vegetable plots, and sausages sold in the local market. Their crimes also extended to their neighbors’ livestock, causing the death of 243 pigs, some 3,100 chickens, and 10 oxen. During the investigation of this rather sordid affair, researchers from the China Medical Research Institute of Preventative Medicine were dispatched to Gaoyao City, and toxicologists from the Peoples’ Liberation Army (PLA) finally identified the poisons from locally obtained samples. Until Du Runqiong was apprehended in November 1995, many of the Gaoyao City’s inhabitants, fearing for their lives, panicked and fled the township. On 22 December 1995 both perpetrators were sentenced to death.
Among Chinese analysts and those responsible for food security in the PRC, there is a general consensus as to what is driving the force behind the chaotic misuse of prohibited rodenticides, particularly tetramine:

- **Marketability.** “Many customers who buy rodenticides like to see fast results; soon after laying down these highly toxic rodenticides, rats quickly die, thus satisfying this need for the consumer.”

- **Ease of manufacture.** Obtaining chemical precursors (ingredients for production) and the synthesis of these compounds are relatively easy.

- **High profitability.** Unscrupulous vendors can double their money by selling a rodenticide like tetramine, where 1 g of pure substance costs about 1 yuan to manufacture, and 1 g of rodenticide fetches about 2 yuan on the open market.

- **Clandestine manufacture and sales.** According to one Chinese account, “Motivated by profits, some rodenticide producers are secretly but clearly producing these rodenticides with tacit approval of the state, some individual entities are doing so without permission. Some are illicit shops, taking very toxic rodenticides and masking them as slow [anticoagulant] poisons or renaming them with monikers such as Sanbudao, “Miraculous Rodenticide”, and other trade names for sale on the market.

- **Regional protectionism.** Corrupt local government officials allow the continued production of banned rodenticides, knowing that they can benefit from increased tax revenues as well as bribes.

- **Weak regulatory enforcement.** While the PRC’s Ministry of Health and the Ministry of Crop Protection have investigative authority, they have no means to levy punishments on violators. Conversely, “the Chinese Department of Market Management has the authority to take punitive measures, but lacks the technical means to test for the highly toxic rodenticides.” (Fan 2002).

**Tetramine brought overseas**

In May 2002, a 15-month-old child in a New York City apartment was playing with a rodenticide powder called Haomao Shuyao [“Good Cat Rat Poison”]. The parents of the child had recently brought the rat poison back from a trip to the PRC. Approximately 15 min after handling the substance, the child developed seizures. Physicians treating the child noted that the original package containing the rodenticide, while intended to market the contents, gave no clear description of what was inside (Fig. 2). There were some markings that read “one fell swoop” and Wendao jisi (“sniff and quickly die”). Even after aggressive treatment with anticonvulsants (including lorazepam and phenobarbital) the child continued seizing and required intubation. The child survived, although a month afterward continued to suffer neurological problems (US CDC 2002).

Packages of tetramine-based rodenticide were also found in an open market in Penang, Malaysia, in late 2002. Sold under the name Sanbudao (“takes three steps and keels over”), these packages of rat poison had been imported from mainland China. A Chinese language article from Malaysia reported how Sanbudao could be purchased in three small pouches for the equivalent of 1 Ringgit, or about US$ 0.25 (UER 2002).

Public health authorities, particularly those serving communities with large overseas Chinese populations should be on the lookout for this dangerous and unregulated rodenticide. Due to the high persistence of tetramine in the environment, it is especially critical that this highly toxic and stable compound be monitored for its presence in the food chain. Although aggressive surveillance is underway in the PRC to find and remove tetramine rat poison from informal markets, it is unknown how effective regulatory enforcement in China has been in removing this hazard. Reports from China have thus far indicated uneven progress in enforcing the prohibition of tetramine and other illicit chemical compounds for sale in open markets (Beijing Daily News 2002).
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